PHARMACOTHERAPY
SELF-ASSESSMENT PROGRAM

PSAP

2017 • BOOK 1

ENDOCRINOLOGY/ NEPHROLOGY

Series Editors
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A Message from the Editors

Every new edition of the Pharmacotherapy Self-Assessment Program (PSAP) presents an opportunity to examine how well we are fulfilling the series mission – to provide pertinent evidence-based updates to enhance and assess the practice skills of pharmacists. As always, we begin by reading comments from our readers. The many users of PSAP are invited to give feedback in two ways: (1) a reader survey available to anyone who purchases a single book or the entire series; and (2) the evaluations that follow each PSAP chapter and learning module. Over the years, these notes have shaped the series by providing practical ideas to improve format, focus content, and enhance learning.

For example, many readers have told us that they find the Patient Care Scenario and Practice Management boxes to be a great assist in translating complex chapter information into real-life clinical practice and thinking through management of patient cases in advance of completing the self-assessment questions. Similarly, the Additional Readings listed at the start of each chapter were a response to learner requests for background in topics they do not often see in everyday practice. Shorter chapters, the Practice Points boxes, hypertext links to Internet resources, video learning elements—these are just some of the features added to PSAP in response to reader comments.

Some things, however, remain the same. Each PSAP release is carefully developed to identify clinically relevant content, solid case-based examples, and fair but challenging self-assessment questions that allow the tester to demonstrate mastery of this important material. To accomplish this—and reflect the changes in practice models, patient populations, and the overall health care environment—PSAP relies on a large volunteer contingent. The dozens of faculty panel chairs, authors, and expert and professional reviewers who contribute to this endeavor do so because of their commitment to the board certification process and the national recognition of clinical pharmacist expertise.

It is our hope that these efforts will build on and further enhance PSAP's reputation as a quality professional development tool for Board Certified Pharmacotherapy Specialists. We extend our heartfelt appreciation to all the faculty panel chairs, authors, and reviewers for lending their time and expertise to the creation of this new series, and to the ACCP Publications staff for their ever-present willingness to help all of us and to guide the development of this new series.

John E. Murphy and Mary W. Lee, series editors

Endocrinology I

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Gestational Diabetes Mellitus

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LEARNING OBJECTIVES

1. Apply data regarding the risks of maternal hyperglycemia to the care of women with gestational diabetes mellitus (GDM).
2. Distinguish the differences between the various screening procedures for GDM.
3. Devise a monitoring plan to maximize maternal and fetal outcomes in patients with GDM.
4. Design an optimal treatment regimen, including nonpharmacologic and pharmacologic therapy, for GDM management.
5. Evaluate the role of oral hypoglycemic agents in GDM treatment.
6. Construct a plan for intra- and postpartum treatment of patients with GDM.

ABBREVIATIONS IN THIS CHAPTER

ACOG	American College of Obstetricians and Gynecologists
ADA	American Diabetes Association
GDM	Gestational diabetes mellitus
LGA	Large for gestational age
NDDG	National Diabetes Data Group
NICE	National Institute for Health and Care Excellence
NPH	Neutral protamine Hagedorn
OGTT	Oral glucose tolerance test

Table of other common abbreviations.

INTRODUCTION

In the past, any hyperglycemia initially detected during pregnancy was considered gestational diabetes mellitus (GDM), regardless of whether the condition actually existed before the pregnancy or continued after the pregnancy. Today, GDM is diabetes that is diagnosed in the second or, more commonly, third trimester and is distinct from type 1 and type 2 diabetes (ADA 2016a). Diabetes developing during the first trimester is generally considered type 2 diabetes, although it can be type 1 or GDM (ADA 2016a). Because of variations in reporting, the population being studied, and the lack of universal diagnostic criteria, the exact prevalence of GDM is difficult to determine. A recent CDC report found prevalence rates of 4.6% and 9.2%, depending on the data sources used (CDC 2014). A history of GDM is the most significant risk factor for GDM. Other risk factors include Asian, Native American, Pacific Islander, African American, or Hispanic ethnicity; BMI of 25 kg/m^2 or greater; diabetes in a first-degree relative; excessive early gestational weight gain (first-trimester weight gain of 2 kg [4.4 lb] plus second-trimester weight gain per week of 0.6 kg [1.3 lb] for underweight, 0.45 kg [1.0 lb] for normal weight, 0.32 kg [0.7 lb] for overweight, and 0.27 kg [0.6 lb] for women with obesity); macrosomia in a previous pregnancy; maternal age older than 35; and weight gain of more than 5 kg (11 lb) since 18 years of age (Garrison 2015).

Women with GDM are often asymptomatic, so screening is important for detection. In a normal pregnancy, insulin resistance develops in the second trimester and continues until birth. The mechanism is not fully understood but is believed to be related to the production of hormones, cytokines, or adipokines by the placenta. Insulin secretion also increases, resulting in normal glucose concentrations. Gestational diabetes typically develops because of preexisting increased insulin

resistance and diminished insulin secretion. During pregnancy, the imbalance between insulin resistance and secretion may lead to hyperglycemia. Gestational diabetes is associated with maternal and fetal complications. Treatment options include nonpharmacologic therapy, insulin, and oral therapy.

MATERNAL AND FETAL COMPLICATIONS

Maternal Complications

Potential maternal complications associated with GDM include gestational hypertension, preeclampsia, and non-elective cesarean delivery. The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study was an international, multicenter study designed to assess the risks of adverse outcomes associated with maternal glucose concentrations (HAPO 2008). Subjects had a one-step 75-g oral glucose tolerance test (OGTT) at 24–32 weeks' gestation. Primary outcomes were birth weight greater than 90th percentile, primary cesarean section delivery, neonatal hypoglycemia, and cord C-peptide greater than 90th percentile. Secondary outcomes included preeclampsia, preterm delivery, shoulder dystocia/birth injury, hyperbilirubinemia, and intensive neonatal care. Results showed a continuous graded relationship of risk, with no distinct thresholds, between maternal glucose concentrations and the primary and secondary outcomes. Cesarean delivery was directly correlated with maternal glycemia, with an overall frequency of 23.7%. Another study found a 19.5% rate of non-elective cesarean delivery in women with GDM, compared with 13.5% in women without diabetes (Gorgal 2012). Results of the HAPO study showed 5.9% of patients had gestational hypertension and 4.8% had preeclampsia. Rates of gestational hypertension and preeclampsia in the general population are 3.6%–9.1% and 1.4%–4.0%, respectively (Roberts 2011). Regarding long-term complications, up to 50% of women with GDM will develop type 2 diabetes later in life. On average, this occurs 22–28 years after pregnancy (England 2009; O'Sullivan 1982). Ethnicity and obesity (BMI > 30 kg/m^2) may play a role in the risk and timing of the subsequent diagnosis of diabetes. For example, as many as 60% of Latino women with GDM may develop diabetes within 5 years (Kjos 1995). Other long-term complications include a 2.5- and 1.7-fold increased risk of developing metabolic syndrome and cardiovascular disease, respectively (Gunderson 2009; Shah 2008).

Fetal Complications

Neonates of women with GDM are at increased risk of macrosomia, which is defined as a birthweight over 4000 g, as well as neonatal hypoglycemia, hyperbilirubinemia, birth trauma, respiratory distress syndrome, and shoulder dystocia (Reece 2010). Macrosomia is the most common fetal complication, with a reported incidence of 15%–45%, followed by hyperbilirubinemia in 10%–13% of neonates (Esakoff 2009; Boulet 2003). Hypoglycemia can occur in 3%–5% of infants as a result of increased fetal insulin production in response to maternal hyperglycemia, which can increase the risk of seizures. Shoulder dystocia is a rare, but serious complication that can lead to brachial plexus injury. Long-term complications of infants born to mothers with GDM include increased risk of impaired glucose tolerance, type 2 diabetes, hypertension, obesity, and dyslipidemia (Mitanchez 2014).

Benefits of Treatment

Few well-designed studies have evaluated the benefit of treating GDM. Trials to date have included treatment strategies of self-monitoring blood glucose, medical nutrition therapy, and insulin. Outcomes data using other treatment modalities are lacking. Treatment of GDM reduces the risk of maternal hypertensive disorders by 40% (Hartling 2013). Rates of cesarean delivery are unaffected by treatment. Evidence on maternal long-term complications, such as type 2 diabetes and obesity, is lacking.

A meta-analysis of five randomized clinical trials found that treating GDM results in a 50% reduction in risk of macrosomia in infants, although the absolute mean difference in birth weight was less than 150 g (Hartling 2013). Risk of shoulder dystocia was reduced by 60%, although the overall events were rare (Hartling 2013). No difference was found

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the pathophysiology of diabetes
- Laboratory testing and self-monitoring values used in diabetes management (e.g., fasting glucose, A1C)
- Common approaches to controlling diabetes – nutritional therapy, exercise, and medications
- Mechanism of action, dosing, and common adverse effects of metformin and glyburide
- Types of insulin (basal, mealtime) and common insulin dosing strategies
- General knowledge of the risk of medication use during pregnancy

Table of common laboratory reference values

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- American Diabetes Association. Standards of medical care in diabetes – 2016. Diabetes Care 2016;39(suppl 1):S94-S98.
- NICE Guideline: Diabetes and pregnancy: management from preconception to the postnatal period.

for neonatal hypoglycemia, birth injury, or risk of eventually developing glucose intolerance. Additional studies of maternal and fetal long-term outcomes are needed because data were insufficient to draw firm conclusions.

Some studies have tried to identify whether any risks are associated with treating GDM. Results from four trials found no increase in small-for-gestational-age neonates, rates of neonatal hypoglycemia, or admission to neonatal ICUs associated with treatment (Hartling 2013). Health care costs were minimally affected by treatment, but the treatment groups did have more prenatal visits.

SCREENING AND DIAGNOSIS OF GDM

Women who are at risk of preexisting diabetes should be screened at their first prenatal visit using the diagnostic criteria for nonpregnant adults. This includes overweight women or women with obesity with at least one additional risk factor, such as physical inactivity, family history of diabetes, high-risk ethnicity, history of GDM, hypertension, or hyperlipidemia (Garrison 2015). Otherwise, screening methods can follow the American Diabetes Association (ADA) or American College of Obstetricians and Gynecologists (ACOG) guidelines.

Screening Methods

Screening and diagnosis of GDM may consist of either a one- or a two-step approach (Figure 1-1). The one-step approach was initially recommended by the ADA in 2011 for use in all pregnant women without preexisting diabetes. It involves a 75-g OGTT at 24–28 weeks' gestation. This was based on recommendations from the International Association of Diabetes and Pregnancy Study Group (IADPSG). The IADPSG recommendations were based primarily on the results of the HAPO study. In reviewing the HAPO study, the IADPSG panel defined diagnostic glucose thresholds on the basis of reaching an OR of 1.75 for adverse outcomes, which led to the creation of the one-step glucose thresholds (IADPSG 2010). The OR of 1.75 was used because it identified the average glucose value at which the adverse outcomes of birth weight, cord C-peptide,

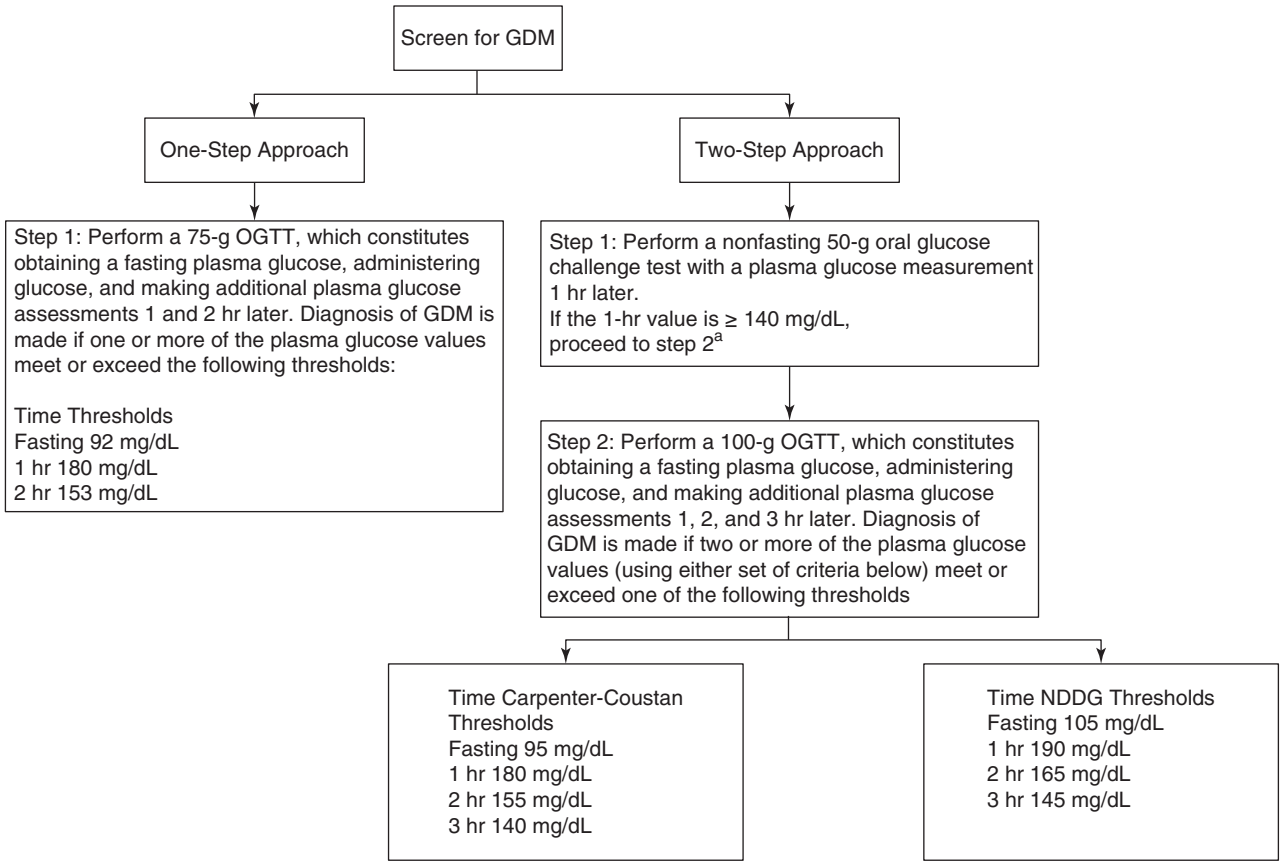

Figure 1-1. Screening and diagnostic criteria for gestational diabetes mellitus

[a]Some clinicians may use a 1-hr threshold of 130 or 135 mg/dL, though the ADA recommends 140 mg/dL. In addition, some clinicians may begin empiric therapy for GDM if the step 1 plasma glucose result is > 200 mg/dL and not proceed to step 2, though the ADA does not include that recommendation in its guidelines.

GDM = gestational diabetes mellitus; NDDG = National Diabetes Data Group; OGTT = oral glucose tolerance test.

Information from: Garrison A. Screening, diagnosis, and management of gestational diabetes mellitus. Am Fam Physician 2015;91:460-7.

and percent body weight were all in the 90th percentile. The two-step approach has been recommended by ACOG and an NIH consensus development program (ACOG 2013).

Controversies Regarding Best Screening Method

The IADPSG and ADA recognize that using the one-step approach would likely increase the number of women with a GDM diagnosis because only one abnormal value is needed for diagnosis. Although this may lead to increased health care costs, the ADA believes that the benefits outweigh these disadvantages. Data are unavailable from randomized controlled trials regarding outcomes for these additional women whose GDM would be diagnosed by the one-step method.

In the two-step approach, two different sets of glucose thresholds exist: Carpenter-Coustan and National Diabetes Data Group (NDDG). The Carpenter-Coustan thresholds are lower than the NDDG thresholds, resulting in higher rates of GDM diagnoses. Use of the Carpenter-Coustan criteria increases diagnosis by 30%–50% (Gokcel 2002; Magee 1993). Comparative trials are limited, making it difficult to recommend one criteria over another. One recent study compared the two diagnostic criteria and their effects on outcomes (Harper 2016b). This was a secondary analysis of a trial involving the treatment of mild GDM in 958 patients. Results showed that treatment with nutritional counseling, dietary therapy, and, in some cases, insulin provided similar reductions in the incidence of pregnancy-induced hypertension, shoulder dystocia, cesarean delivery, and macrosomia, regardless of which two-step diagnostic criteria were used. Clinicians and institutions should select one criteria to use consistently, with local rates of diabetes and availability of resources for managing GDM factored into that decision.

A recent systematic review analyzed 38 studies to assess different diagnostic thresholds for GDM on maternal and fetal outcomes in the absence of treatment for GDM. The results showed that women with GDM, regardless of the diagnostic criteria used, consistently had higher rates of cesarean section, shoulder dystocia, and large for gestational age (LGA) infants. Macrosomia was significantly higher with the two-step approach, but not the one-step approach. The authors concluded that higher glucose thresholds did not consistently have higher maternal or fetal risks, and further research is needed to determine which diagnostic criteria are associated with the best outcomes.

MONITORING IN GDM

Blood Glucose Monitoring

Once a woman has a diagnosis of GDM, routine glucose monitoring should begin. Evidence is lacking regarding the optimal frequency of testing, but the general recommendation is to monitor four times a day (ACOG 2013). This would consist of daily monitoring of fasting glucose and 1 or 2 hours after each meal. Data are insufficient regarding whether 1- versus 2-hour postprandial monitoring is superior. Postprandial glucose control is associated with better overall glycemic control and may be more predictive of maternal and fetal complications. Individuals with GDM that is diet controlled can monitor less often.

Glucose Goals and Other Monitoring Values

Observational studies show that A1C concentrations less than 6%–6.5% are associated with the lowest rates of fetal complications, but trials have not evaluated the risk-benefit of achieving these targets. Hemoglobin A1C concentrations during normal pregnancy fall by as much as 0.5% because of increased RBC turnover (Nielsen 2004). Furthermore, because postprandial glucose is a better indicator of risk of complications, A1C is not as useful. Suggested glycemic targets for patients with GDM, which vary slightly among the various guidelines, are outlined in Table 1-1.

NONPHARMACOLOGIC MANAGEMENT

Nutritional Therapy

Medical nutrition therapy is the cornerstone of treatment for GDM (Metzger 2007). Dietary intervention, in combination with insulin therapy as needed, reduces the risk of LGA

Table 1-1. Recommended Glycemic Targets for Patients with Gestational Diabetes

Guideline	Fasting Glucose (mg/dL)	1-Hr Postprandial Glucose (mg/dL)	2-Hr Postprandial Glucose (mg/dL)
ACOG	≤ 95	< 140	< 120
ADA	≤ 95	≤ 140	≤ 120
Endocrine Society	≤ 95[a]	≤ 140	≤ 120
NICE	< 95	< 140	< 115

[a]The Endocrine Society suggests a lower fasting glucose target of ≤ 90 mg/dL if it is attainable without significant hypoglycemia.
NICE = National Institute for Health and Care Excellence.

infants, fetal macrosomia, preeclampsia, and serious perinatal complications (Landon 2009; Crowther 2005). All women with GDM should receive dietary counseling at the time of diagnosis, preferably provided by a registered dietitian or nutritionist experienced in GDM management. The goals of dietary modification in GDM are to attain the desired level of glycemic control; provide adequate weight gain, which contributes to maternal and fetal well-being; and prevent the development of ketosis (ACOG 2013).

Suggested weight gain during pregnancy for patients with GDM varies according to the pre-pregnancy BMI. The ADA recommends a weight gain of 6.8–11.3 kg (15–25 lb) for overweight women and 4.5–9.1 kg (10–20 lb) for women with obesity (ADA 2016b), and the Endocrine Society suggests similar gestational weight gain, as outlined in the Institute of Medicine (IOM) revised guidelines for weight gain during pregnancy (Blumer 2013; Rasmussen 2009). Table 1-2 provides an overview of recommendations for weight gain in pregnancy, together with suggested caloric intake. Excessive weight gain is associated with a greater risk of fetal macrosomia and should be avoided. A large retrospective cohort study showed that women with GDM who followed IOM guidelines for weight gain had improved perinatal outcomes, and women who had excessive weight gain were more likely to have an LGA infant, preterm delivery, or cesarean delivery (Cheng 2008b). Conversely, women who gained less weight than recommended had a greater risk of delivering a small-for-gestational-age infant. In general, women with obesity women should reduce their pre-pregnancy daily caloric consumption by about 30% while maintaining a minimum caloric intake of 1600–1800 kcal per day (Blumer 2013; ADA 2008). More severe restriction of caloric intake may result in ketosis. Weight loss during pregnancy is not generally recommended (ADA 2008). Weekly weight checks can be used to identify excessive or insufficient weight gain.

Medical nutrition therapy for women with GDM should emphasize distribution of calories, with a focus on restriction of carbohydrates. The ACOG guidelines recommend a caloric distribution of 33%–40% carbohydrates, 20% protein, and 40% fat (ACOG 2013). Strong evidence for the optimal proportion of carbohydrates in GDM is lacking, and the Endocrine Society suggests a slightly less restrictive carbohydrate intake of 35%–45% of total calories (Blumer 2013). Other sources recommend a minimum intake of 175 g of carbohydrates per day, although this is greater than the recommended daily carbohydrate consumption (130 g) for nonpregnant women (Blumer 2013; ADA 2008; IOM 2002). Regardless of the strategy used to determine initial carbohydrate intake in GDM, adjustment of carbohydrate consumption should be ongoing and based on clinical measures such as blood glucose concentrations, ketone concentrations, and weight gain (ADA 2008).

A typical daily meal plan for women with GDM includes three small to moderate-sized meals and two to four snacks, one of which should be at bedtime to prevent the development of ketosis overnight (ADA 2008). Meal plans should consider cultural preferences as well as desired weight gain and level of physical activity (Metzger 2007). A suggested recommendation for caloric distribution across meals and snacks consists of 10% of total calories at breakfast, 30% at lunch, 30% at dinner, and 30% divided between the snacks. In general, carbohydrate intake should be distributed throughout the day to reduce postprandial hyperglycemia, and protein should be included with all meals and snacks to promote satiety. Glucose may be more difficult to control in the morning due to the dawn phenomenon. Therefore, women with GDM may require lower carbohydrate consumption to attain desired glucose concentrations after breakfast compared with other meals. Patients with GDM should be trained in carbohydrate counting, and blood glucose concentrations should be interpreted in the context of food logs that document carbohydrate intake (Metzger 2007). When insulin therapy is needed, consistency of carbohydrate intake with meals and snacks is an important focus (ADA 2008).

Table 1-2. Recommendations for Weight Gain and Caloric Requirements During Pregnancy

Pre-pregnancy BMI (kg/m^2)	Total Weight Gain	Rates of Weight Gain[a] 2nd and 3rd Trimesters	Caloric Requirements
	Range, lb	Mean (range), lb/wk	Range, kcal/kg/day[b]
Underweight (< 18.5)	28–40	1 (1–1.3)	Up to 40
Normal weight (18.5–24.9)	25–35	1 (0.8–1)	30
Overweight (25.0–29.9)	15–25	0.6 (0.5–0.7)	22–25
Obese (≥ 30.0)	11–20	0.5 (0.4–0.6)	12–14

[a]Calculations assume a 1.1- to 4.4-lb weight gain in the first trimester.

[b]Present pregnant weight.

Information from: Rasmussen KM, Yaktine AL; Institute of Medicine (U.S.). Committee to Reexamine IOM Pregnancy Weight Guidelines. Weight Gain During Pregnancy: Reexamining the Guidelines. Washington, DC: National Academies Press, 2009.

In addition to the amount of carbohydrates ingested, the type of carbohydrates is important. Intake of complex carbohydrates is preferred to intake of simple carbohydrates because complex carbohydrates are less likely to cause postprandial hyperglycemia (ACOG 2013). Food sources that are higher in complex carbohydrates tend to have a lower glycemic index, which blunts the rise in postprandial glucose.

A randomized trial of 63 women with GDM compared a low-glycemic index diet with a conventional high-fiber diet with a higher glycemic index (Moses 2009). Women receiving the higher glycemic index diet were significantly more likely to require the addition of insulin therapy. Furthermore, insulin treatment was avoided in about half of these women when they changed to the low-glycemic index diet. Likewise, a systematic review and meta-analysis that included nine randomized controlled trials and 884 women with GDM showed that a low-glycemic index diet was associated with a lower rate of insulin use (relative risk of insulin use 0.77) and lower birth weight infants (mean weight difference –161.9 g) (Viana 2014). In the same study, diets classified as low carbohydrate or characterized by moderate energy restriction (about 33% reduction in caloric intake) were not associated with changes in insulin use or birth weight. None of the diets had a significant effect on maternal or neonatal outcomes such as maternal weight gain, frequency of cesarean delivery, or incidence of fetal macrosomia.

Another small study (n=52) examined the effects of the Dietary Approaches to Stop Hypertension (DASH) diet in women with GDM (Asemi 2014). Women randomized to the DASH diet for 4 weeks during pregnancy were significantly less likely to require cesarean delivery (46.2% vs. 80.8%) or addition of insulin therapy (23% vs. 73%) than were women randomized to the control diet (45%–55% carbohydrates, 15%–20% protein, and 25–30% fat). Infant birth weights in the DASH diet group were also significantly lower (3222.7 g vs. 3818.8 g). The DASH diet is similar to a low-glycemic index diet, with its emphasis on fruits, vegetables, whole grains, and lean meats. According to the available evidence, patients with GDM should be encouraged to select carbohydrate sources with a low glycemic index, such as whole grains, fruits, and vegetables (Box 1-1).

Box 1-1. Glycemic Index of Various Foods

Low glycemic index

- Carrots
- Corn
- Fruits (most)
- Lima beans
- Oat bran
- Peas
- Steel-cut oatmeal
- Stone-ground whole wheat bread
- Sweet potatoes

Moderate glycemic index

- Brown rice
- Couscous
- Quick oats
- Pita bread
- Rye bread
- Whole wheat bread
- Wild rice

High glycemic index

- Bagel
- Bran flakes
- Corn flakes
- Instant oatmeal
- Melon
- Pineapple
- Popcorn
- Pretzels
- White bread
- White rice

Information from: American Diabetes Association. Glycemic Index and Diabetes [homepage on the Internet]. 2013.

Physical Activity

Together with medical nutrition therapy, physical activity is a key component in initial GDM management. Physical activity improves insulin sensitivity and reduces both fasting and postprandial glucose concentrations in patients with diabetes. The ADA, ACOG, and Endocrine Society guidelines recommend a program of moderate exercise consisting of 30 minutes most days of the week for women with GDM who have no medical or obstetric contraindications to physical activity (ACOG 2013; Blumer 2013; Colberg 2010). Examples of moderate exercise include brisk walking, recumbent bicycling, or 10 minutes of seated arm exercises after each meal.

Although many randomized controlled trials support the benefits of physical activity in nonpregnant adults with diabetes, evidence of improved outcomes in GDM is limited. A small randomized trial of 19 women with GDM examined the effects of diet (20% protein, 40% carbohydrate, and 40% fat) and exercise compared with diet alone for 6 weeks (Jovanovic 1989). The exercise regimen consisted of 20 minutes of physical activity three times weekly using an arm ergometer (arm cycle or arm crank) to maintain heart rate in the desired range. Participants in the exercise group had significantly lower fasting glucose (70.1 ± 6.6 vs. 87.6 ± 6.2 mg/dL) and 1-hour plasma glucose concentrations (105.9 ± 18.9 vs. 187.5 ± 12.9 mg/dL) after a 50-g oral glucose challenge. Another small randomized trial evaluated a regimen of diet and exercise consisting of cycling for 45 minutes three times weekly compared with a regimen of diet and insulin therapy (Bung 1991). Mean glucose concentrations, rates of cesarean delivery, infant birth weights, and incidence of fetal macrosomia were comparable between the two groups.

In 2006, a systematic review and meta-analysis of four trials involving 114 women with GDM found that glucose control was improved in patients who participated in an exercise program

such as an arm ergometer or cycling for 20–45 minutes three times weekly compared with those without a specific exercise regimen (Ceysens 2006). Maternal and neonatal outcomes such as need for insulin therapy and fetal macrosomia did not differ in the exercise group. The authors concluded that the evidence was insufficient to advocate for or against an exercise program for women with GDM and recommended further study to better determine the effects of exercise on maternal and fetal outcomes in GDM. Although evidence is limited for improvement in maternal and perinatal outcomes, a regimen of moderate exercise helps control maternal blood glucose and should be recommended for most women with GDM.

DRUG THERAPY FOR GDM

Suggested Thresholds for Initiation

With appropriate lifestyle modification, 70%–85% of women with GDM can achieve adequate glucose control (ADA 2016b). Drug therapy should be considered when medical nutrition therapy and moderate physical activity fail to achieve glucose goals within 1–2 weeks. Little consensus exists regarding the threshold glucose values that should trigger initiation of drug therapy. A systematic review and meta-analysis found no evidence to support that maternal and infant outcomes were affected by the glucose concentration at initiation of drug therapy for GDM (Nicholson 2008).

One approach is to initiate pharmacologic therapy if most glucose values within a 1-week period are elevated (Landon 2009). The ACOG guidelines recommend initiating drug therapy if fasting glucose concentrations are routinely greater than 95 mg/dL, or 1- or 2-hour postprandial concentrations are routinely 140 mg/dL and 120 mg/dL or greater, respectively (ACOG 2013). Another method is to begin drug therapy if two or more values at the same meal (e.g., post-breakfast or post-lunch) in a 2-week period exceed desired glucose concentrations by more than 10 mg/dL (Moore 2010). A third approach involves initiating drug therapy if two or more fasting or postprandial blood glucose values exceed 100 mg/dL or 126 mg/dL, respectively, in a 2-week period (Crowther 2005). Overall, a defined threshold of initiation for drug therapy in GDM does not exist, and clinicians should consider the severity and frequency of hyperglycemia, fetal growth, and patient factors when deciding to initiate pharmacotherapy (Garrison 2015; ACOG 2013).

Insulin

Human insulin crosses the placenta in insignificant amounts and is considered safe for use in pregnancy. Both the ADA and ACOG guidelines recommend insulin as a first-line treatment for GDM uncontrolled by nutritional therapy. The National Institute for Health and Care Excellence (NICE) guideline advises initial treatment with insulin, either with or without metformin, for any patient with a fasting glucose of 7 mmol/L (126 mg/dL) or greater at diagnosis (NICE 2015). The NICE guideline also suggests consideration of insulin, either with or without metformin, for women with complications of GDM such as macrosomia and a fasting glucose of 6.0–6.9 mmol/L (108–125 mg/dL).

Options for basal insulin coverage in GDM treatment include intermediate-acting neutral protamine Hagedorn (NPH) insulin and the long-acting analogs insulin glargine and insulin detemir (Table 1-3). Insulin degludec has not been studied in pregnant women. Because NPH insulin was used in initial studies of GDM, it is the standard with which the long-acting insulin analogs have been compared, and several guidelines continue to recommend its use. Both ACOG and the Endocrine Society suggest the use of NPH insulin for the treatment of women with GDM (ACOG 2013; Blumer 2013), whereas the ADA does not specify a preferred basal insulin (ADA 2016b). In the general nonpregnant population, long-acting insulin analogs are associated with a lower risk of hypoglycemia than NPH insulin, making them an option for GDM management. However, as with any agent for use in pregnant women, the longer-acting insulin analogs needed to overcome safety concerns before use could be endorsed in this specialty population.

Table 1-3. Insulin Preparations Used in the Management of Gestational Diabetes

Type of Insulin Preparation	Onset of Action (hr)	Peak of Action (hr)	Duration (hr)
Mealtime insulin			
Insulin aspart	0.25	1–3	3–5
Insulin lispro	0.25–0.5	1–3	3–5
Regular insulin	0.5–1	2–3	5–7
Basal insulin			
Insulin detemir	1–2	No pronounced peak	8 to ≥ 24
Insulin glargine	1–2	No pronounced peak	11 to ≥ 24
NPH insulin	1–2	4–12	10–19 (up to 24)

Use of insulin detemir in pregnancy was first investigated in women with type 1 diabetes. In a randomized open-label trial of 310 pregnant patients with type 1 diabetes, insulin detemir was compared with NPH insulin, both used in combination with mealtime insulin in a basal-bolus regimen (Hod 2014). Overall, maternal and perinatal outcomes were similar in both groups. No significant safety concerns were identified in the insulin detemir group. In addition, a meta-analysis examining the safety of insulin analogs in pregnancy concluded that the risks of neonatal hypoglycemia or LGA neonates with insulin detemir compared with NPH insulin were not increased in the treatment of type 1 diabetes in pregnancy (Lv 2015). A recent randomized trial of 85 women with GDM found insulin detemir noninferior to NPH insulin for glucose control (Herrera 2015). The trial was not powered sufficiently to detect differences in perinatal outcomes or maternal weight gain.

The Endocrine Society suggests use of insulin detemir in women with known or potential problematic hypoglycemia with NPH insulin (Blumer 2013). In the United States, insulin detemir is rated FDA pregnancy risk category B, and the European Medicines Agency permits its use during pregnancy. The FDA has instituted a change in the pregnancy information required within prescription drug labeling (Pregnancy and Lactation Labeling Rule – PLLR); the current pregnancy risk categories are gradually being phased out in favor of more comprehensive information. Currently, however, the pregnancy risk categories are still in the labeling of many prescription drug products.

A concern with the use of insulin glargine in pregnancy is its increased affinity for the insulin-like growth factor (IGF-1) receptor (Pollex 2011). The IGF-1 receptor is structurally similar to the insulin receptor, and insulin analogs have modifications in amino acid sequence or structure that may increase or diminish the binding affinity for IGF-1 receptors (Jovanovic 2007). Insulin glargine has a 6-fold affinity for the IGF-1 receptor compared with human insulin, and insulin detemir has about one-sixth the affinity. During pregnancy, IGF-1 plays a role in implantation and mediates the effects of human placental growth hormone on the fetus. Thus, disruption of the normal function of IGF-1 raises concerns of potential enhanced mitogenic activity. However, in therapeutic doses, insulin glargine is unlikely to cross the placenta, and studies to date have not shown an increased fetal risk with the use of this agent during pregnancy.

A systematic review and meta-analysis of eight studies involving 702 women with pregestational diabetes (existing type 1 or type 2 diabetes before pregnancy) or GDM who received insulin glargine in pregnancy concluded that fetal outcomes did not differ significantly from those of women treated with NPH insulin (Pollex 2011). A second meta-analysis examining the use of insulin glargine in eight observational studies of pregestational diabetes or GDM showed no significant difference in birth weight, neonatal outcomes, or severe maternal hypoglycemia compared with NPH insulin (Lv 2015). In summary, randomized controlled trials using insulin glargine in GDM are lacking, and insulin glargine should only be used if the benefits outweigh the risk of adverse effects to the mother and fetus.

The rapid-acting analogs insulin aspart and insulin lispro are preferred to regular insulin for mealtime coverage (ACOG 2013). Both analogs improve postprandial glucose control compared with regular insulin and may have a reduced risk of delayed postprandial hypoglycemia (Metzger 2007). The analogs are also more convenient to administer preprandially, as opposed to regular insulin, which should be administered 30 minutes before meals for optimal postprandial coverage (Cheng 2008a). Like the long-acting analogs, the rapid-acting analogs were first studied in pregnancy in type 1 diabetes.

A randomized, open-label trial of 322 patients with type 1 diabetes showed that perinatal outcomes and maternal glucose control with insulin aspart were comparable with regular insulin when used in a basal-bolus regimen (Hod 2008). Similarly, in a meta-analysis of six randomized controlled trials of women with pregestational diabetes or GDM (n=1143), insulin aspart appeared to be as safe as regular insulin, with no significant differences in the rate of fetal macrosomia or cesarean delivery (Lv 2015). The same meta-analysis included a review of nine observational studies of women with pregestational diabetes or GDM (n=1561) treated with insulin lispro or regular insulin and concluded that insulin lispro was associated with a higher rate of LGA infants but a lower risk of severe maternal hypoglycemia than regular insulin. Use of insulin lispro was not associated with an increased rate of fetal macrosomia or cesarean delivery (Lv 2015).

Glulisine is the only rapid-acting insulin without human data in pregnancy. As a result, glulisine is the only rapid-acting analog rated as FDA pregnancy risk category C; aspart and lispro are category B. The Endocrine Society states that insulin glulisine should not be used in pregnancy because it offers no added benefit over other rapid-acting analogs (Blumer 2013). According to the available evidence, the rapid-acting insulin analogs, aspart and lispro, have efficacy and safety comparable with regular insulin. They are preferred in GDM management because of the convenience of mealtime administration and potentially lower risk of delayed hypoglycemia.

Insulin requirements can vary widely during pregnancy, particularly during the second trimester when insulin resistance may rise rapidly (ADA 2016b). Insulin resistance continues to increase into the third trimester and may plateau or diminish slightly near the end of pregnancy. Because most women receive a diagnosis of GDM late in the second trimester or early in the third trimester, variability in insulin requirements should be considered. For women who have mild fasting hyperglycemia, an injection of intermediate- or long-acting insulin (0.15–0.2 unit/kg) at bedtime can be used to control elevated fasting glucose. Mild postprandial elevations in glucose can typically be managed with administration of 2–4 units of rapid-acting insulin before meals. Alternatively, elevated

glucose after lunch may be treated with an intermediate-acting insulin before breakfast (Cheng 2008a).

For women with marked hyperglycemia, several daily injections provide optimal glucose control. A typical starting dose of insulin is 0.7–1 unit/kg/day (Table 1-4), administered in divided doses (ACOG 2013; Hone 2010). Higher insulin doses may be required in women with obesity or multiple gestation pregnancies. Once the total daily insulin dose is calculated, 50% is administered as basal insulin using NPH or long-acting insulin analogs, and the remaining 50% is administered in three preprandial injections of rapid-acting insulin (Hone 2010). According to initial studies with NPH in pregnancy, some sources recommend that if NPH is selected as the basal insulin, it should be divided into three equal doses given before breakfast, before dinner, and at bedtime (Hone 2010). However, a twice-daily regimen of NPH is commonly used for basal control. For women with limited financial resources, a regimen of NPH and regular insulin may be more affordable. Regardless of the initial regimen, the dose should be titrated often, using data from self-monitoring of blood glucose.

Metformin

Because many women with GDM have mild hyperglycemia, treatment with oral medications such as metformin is also an acceptable option when medical nutrition therapy and exercise fail to control glucose adequately. Metformin improves peripheral insulin sensitivity and is not known to cause weight gain or hypoglycemia when used alone (Rowan 2008). In addition, metformin has been used in patients with polycystic ovary syndrome to increase ovulation and enhance fertility, and it may be continued until the end of the first trimester in an attempt to reduce the rate of spontaneous abortion (ACOG 2013; Metzger 2007). Metformin crosses the placenta, and initially, there was concern about using metformin in pregnancy when a small retrospective cohort study of 118 patients found an increased incidence of preeclampsia and perinatal loss with metformin compared with treatment with sulfonylureas or insulin (Hellmuth 2000). These findings were based on patients with GDM or type 2 diabetes who were treated with oral hypoglycemic agents or insulin during pregnancy at a single site in Denmark between 1966 and 1991. However, more recent studies have not noted similar safety concerns with metformin use in pregnancy, and the drug is currently rated as FDA pregnancy risk category B. Management of GDM is an off-label indication of metformin.

Table 1-4. Suggested Starting Dose of Insulin in Gestational Diabetes

Weeks' Gestation	Insulin Dose[a] (unit/kg/day)
0–12	0.7
13–28	0.8
29–34	0.9
35–40	1.0

[a]Present pregnancy weight.

Information from: Hone J, Jovanovic L. Approach to the patient with diabetes during pregnancy. J Clin Endocrinol Metab 2010;95:3578-85.

In 2008, the Metformin in Gestational Diabetes (MiG) trial investigators published the first large randomized controlled trial (n=751) examining metformin use as compared to insulin in GDM treatment (Rowan 2008). The metformin dose was initiated at 500 mg once or twice daily with food and titrated over 1–2 weeks, depending on glycemic goals, to a maximum daily dosage of 2500 mg. No significant differences occurred between the metformin- and insulin-treated groups in the composite outcome of neonatal complications, which included a composite measure of neonatal hypoglycemia, respiratory distress, need for phototherapy, birth trauma, 5-minute Apgar score less than 7, and prematurity. The incidence of preterm delivery (less than 37 weeks' gestation) was significantly higher with metformin (12.1% vs. 7.6%). As might be expected, the risk of severe neonatal hypoglycemia was significantly lower in the metformin group (3.3% vs. 8.1%). About 45% of the women in the metformin group needed supplemental insulin therapy to achieve glycemic targets (Rowan 2008).

A second randomized controlled trial compared metformin with glyburide for GDM treatment (Moore 2010). Seventy-four women were randomized to glyburide and 75 to metformin, and the primary outcome was glucose control. For patients who were able to maintain glucose control with either drug alone, the mean fasting or 2-hour postprandial glucose concentrations were similar. However, about twice as many women in the metformin group (34.7%) required supplemental insulin to achieve glucose control compared with the glyburide group (16.2%). Mean birth weights were lower in the metformin group, but the study was underpowered to explore other secondary outcomes.

A systematic review and meta-analysis examined maternal and fetal outcomes with metformin compared with insulin in six randomized controlled trials, which included 1362 patients with GDM (Balsells 2015). Maternal outcomes were improved with metformin compared with insulin, with less maternal weight gain and a lower risk of pregnancy-induced hypertension. Fetal outcomes, however, included a lower gestational age at delivery (−0.16 weeks) and an increased risk of preterm delivery with metformin (risk ratio 1.50). Although it did not reach statistical significance, there was a trend toward less neonatal hypoglycemia with metformin. On average, 33.8% of women in the metformin group required supplemental insulin. These findings were supported by an earlier meta-analysis that evaluated a similar set of trials (Gui 2013).

In the earlier meta-analysis, the effects of metformin compared with glyburide in women with GDM were also evaluated

(Balsells 2015). Only two randomized controlled trials (n=349) were available that had studied the two drugs head-to-head for GDM management. Compared with glyburide, metformin was associated with less maternal weight gain (–2.06 kg). In addition, fetal outcomes included lower birth weight, less macrosomia (risk ratio 0.33), and a lower incidence of LGA infants in the metformin group. The treatment failure rates were 26.8% and 23.5% with metformin and glyburide, respectively. Given this analysis, the investigators concluded that glyburide was inferior to metformin in GDM management.

Recommendations for the role of metformin in GDM treatment differ, according to the various guidelines. The ACOG guidelines recommend metformin as an appropriate first-line therapy for GDM management, and the NICE guideline also supports metformin as initial therapy in women with GDM and a fasting glucose below 7 mmol/L (126 mg/dL) at diagnosis (NICE 2015; ACOG 2013). In contrast, the Endocrine Society suggests metformin as an alternative in women who refuse or have contraindications to insulin or glyburide (Blumer 2013). The rationale for this recommendation includes the higher failure rate of metformin and the unknown long-term safety profile in offspring of women treated with metformin. The ADA recommends insulin as a first-line agent and proposes metformin as an acceptable alternative if glucose control is sufficient (ADA 2016b). The ADA cites the slightly higher risk of prematurity and unknown long-term effects on offspring as concerns with metformin use in GDM.

Although metformin has an acceptable safety profile with short-term use in GDM management, it crosses the placenta readily, and the long-term effects of fetal exposure to an insulin-sensitizing agent are unknown. To address these concerns, the MiG trial investigators assessed the potential effects on growth of children exposed to metformin in utero (Rowan 2011). Offspring of women who participated in the MiG trial had body composition measurements at 2 years of age. Overall, the children born to mothers treated with metformin did not differ in height, weight, total fat, or percent body fat compared with children whose mothers were treated with insulin. However, offspring exposed to metformin had a higher amount of subcutaneous fat, as noted in the upper arm circumference and biceps and subscapular skinfolds. The implications of this change in fat distribution are unclear. For instance, it is unknown whether an increase in subcutaneous fat deposition translates to less visceral fat. The intent of the MiG investigators is to reassess these children at later points in life. Thus, additional data are needed to fully assess the long-term safety and outcomes in offspring exposed to metformin in utero. Women who are prescribed metformin for GDM management should be counseled that metformin crosses the placenta and that the long-term effects of fetal exposure to this agent are unknown.

Glyburide

Glyburide has been extensively studied for GDM management. Glyburide is the only sulfonylurea that crosses the placenta to a minimal extent, likely because of high protein binding (Metzger 2007). Depending on the manufacturer, glyburide is rated as FDA pregnancy risk category B or C. Management of GDM is an off-label use of glyburide. When used in GDM treatment, the initial glyburide dose is typically 2.5–5 mg once daily in the morning. The dose is titrated according to glucose readings to a maximum of 20 mg daily, usually given in two divided doses (ACOG 2013). For best efficacy, glyburide should be administered 30–60 minutes before meals, and the drug's activity should be carefully balanced with meals and snacks to minimize the risk of hypoglycemia (Caritis 2013). Supplemental insulin therapy may be required in 5%–20% of patients with GDM managed with glyburide. When selecting therapy, practitioners should consider that glyburide may be less effective in women with higher fasting glucose concentrations at diagnosis and those with a history of GDM or GDM diagnosed before 26 weeks' gestation (Harper 2016a). Although clinical studies show that adequate glucose control can be attained in most patients with GDM treated with glyburide, recent safety analyses have raised concerns about glyburide as a first-line therapy for GDM.

An initial randomized controlled trial that investigated glyburide use in 404 women with GDM found no significant differences in glycemic control or perinatal outcomes in the glyburide-treated group compared with the insulin-treated group, although the study was underpowered to detect differences in less common neonatal complications (Langer 2000). A large retrospective cohort study of women with GDM enrolled in the Sweet Success California Diabetes and Pregnancy Program (n=10,682) examined perinatal outcomes in women who were treated with glyburide compared with insulin therapy (Cheng 2012). In the Sweet Success program, 19.4% of women received glyburide and 80% received insulin therapy. Treatment with glyburide was associated with an increased risk of birth weight greater than 4000 g and admission to the neonatal ICU. A second retrospective cohort study, which investigated perinatal outcomes in GDM through review of a large insurance claims database, had similar findings (Camelo Castillo 2015). Neonates of mothers treated with glyburide (n=4982) had a higher risk of neonatal ICU admission, respiratory distress, and LGA. Although noted study limitations included lack of information on the level of glycemic control and maternal obesity as possible confounding factors, the data suggested the need for additional study regarding the safety of glyburide in GDM. Of interest, the authors noted that the frequency of glyburide use for GDM in the claims database had increased from 7.4% in 2000 to 64.5% in 2011 (Camelo Castillo 2014). A recent systematic review and meta-analysis of seven randomized controlled trials that compared glyburide with insulin in GDM management showed that glyburide was associated with a higher mean birth weight (mean difference 109 g) and an increased risk of macrosomia and neonatal hypoglycemia (Balsells 2015). Given these results and supportive data from

prior analyses, glyburide should not be used not be used as a first-line agent in GDM management if insulin or metformin is available.

The ADA continues to endorse insulin as a first-line agent for GDM management, stating that glyburide may be inferior to insulin and metformin because of the increased risk of macrosomia and neonatal hypoglycemia (ADA 2016b). The NICE guideline recommends consideration of glibenclamide (glyburide) in women intolerant of metformin therapy or those with poor glycemic control on metformin alone who refuse insulin therapy (NICE 2015). In contrast, ACOG supports glyburide as a suitable first-line treatment for GDM, and the Endocrine Society recommends glyburide as an acceptable alternative to insulin therapy, although these recommendations were made before the more recent glyburide safety data (ACOG 2013; Blumer 2013). Women with GDM who are initiated on glyburide should be counseled about the potential increased risk of macrosomia and neonatal hypoglycemia, as well as the risk of maternal hypoglycemia and strategies for managing hypoglycemia with this agent. In addition, they should be informed that glyburide crosses the placenta in trace amounts, and long-term safety data are lacking.

Other Agents

Data with other oral and injectable agents in GDM treatment are limited. The α-glucosidase inhibitor acarbose was studied in one small trial, which randomized women with GDM to receive acarbose (n=19), insulin (n=27), or glyburide (n=24) (Bertini 2005). Eight patients treated with acarbose (42.1%) did not achieve glycemic control, compared with five of the glyburide-treated patients (20.8%). The incidence of LGA infants was 10.5%, 25%, and 3.7% in the acarbose, glyburide, and insulin groups, respectively. In an observational cohort study of women exposed to medications in pregnancy, five women reported treatment with acarbose early in pregnancy, and two of the women had miscarriages (Wilton 1998). Given these data and the GI adverse effect profile of acarbose, it cannot be recommended for GDM treatment. Other agents such as the meglitinides, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, and

Patient Care Scenario

A 34-year-old Hispanic woman at 30 weeks' gestation in her first pregnancy presents for a follow-up visit. She was given a diagnosis of GDM at 28 weeks' gestation, and her fasting glucose at diagnosis was 107 mg/dL. At that time, she was counseled to begin nutritional therapy and a moderate exercise regimen. Given the following glucose values over the past week, what is the best option for GDM management in this patient?

Fasting glucose (mg/dL): 94, 102, 98, 97, 100, 93, 107
One hour after breakfast: 137, 140, 142, 135
One hour after lunch: 132, 141, 148
Two hours after dinner: 129, 120, 118, 124

ANSWER

Drug therapy for GDM is recommended if lifestyle modifications fail to achieve adequate glucose control within 1–2 weeks. The ACOG guidelines support initiating drug therapy for GDM if fasting glucose concentrations routinely exceed 95 mg/dL (five of seven during the past week), 1-hour glucose concentrations routinely exceed 140 mg/dL (three of seven), or 2-hour glucose concentrations routinely exceed 120 mg/dL (two of four). Therefore, the patient is a candidate for GDM drug therapy.

Insulin, glyburide, and metformin are alternatives for GDM management, and given the patient's mild hyperglycemia, an oral medication is a reasonable first choice. The ACOG guidelines recommend metformin as an appropriate first-line therapy for GDM management. The NICE guideline also supports metformin as initial therapy in women with GDM and a fasting glucose below 126 mg/dL at diagnosis, which is consistent with the data available for this patient. Although glyburide might be considered for GDM, recent data have generated concerns regarding its use as a preferred therapy for GDM. In addition to the potential for maternal hypoglycemia, glyburide has been associated with an increased risk of fetal macrosomia and neonatal hypoglycemia compared with insulin. The NICE guideline recommends consideration of glyburide in women intolerant of metformin therapy.

Metformin should be initiated at a dose of 500 mg once or twice daily and titrated over 1–2 weeks, depending on glucose concentrations and patient tolerance. If target glucose concentrations are not achieved with metformin, insulin should be added. The patient should be counseled that many women with GDM treated with metformin may require supplemental insulin to obtain adequate glucose control (20%–45%). In addition, metformin crosses the placenta, and the long-term effects of fetal exposure of metformin are unknown.

1. American College of Obstetricians and Gynecologists (ACOG) Committee on practice bulletins-obstetrics. Practice bulletin no. 137: gestational diabetes mellitus. Obstet Gynecol 2013;122:406-16.
2. NICE Guideline: Diabetes and Pregnancy: Management from Preconception to the Postnatal Period. 2015. Available at https://www.nice.org.uk/guidance/ng3/resources/diabetes-in-pregnancy-management-of-diabetes-and-its-complications-from-preconception-to-the-postnatal-period-51038446021.
3. Balsells M, Garcia-Patterson A, Sola I, et al. Glibenclamide, metformin and insulin for the treatment of gestational diabetes: a systematic review and meta-analysis. BMJ 2015;350:h102.

sodium glucose cotransporter-2 inhibitors have limited or no human data in pregnancy and should not be considered for GDM management.

OTHER MANAGEMENT STRATEGIES

Fetal Assessment

The need for other management strategies often depends on the severity of maternal hyperglycemia and the ease of glucose control. The ACOG guidelines recommend antenatal testing for poor glycemic control because these pregnancies have a higher likelihood of complications such as stillbirth (ACOG 2013). In general, antenatal testing is usually done in women who require oral drug therapy or insulin for GDM management (Garrison 2015). However, no consensus exists regarding the use of antenatal testing in women with GDM well controlled with nutritional therapy. Omission of antenatal testing in this population may be reasonable if there are no other pregnancy complications (e.g., preeclampsia) or other risk factors for poor pregnancy outcomes, such as advanced maternal age or previous stillbirth.

Specific guidelines detailing the type and timing of antenatal assessments in women with GDM are not available, and ACOG recommends that antenatal testing be conducted in accordance with local standards of practice (ACOG 2013). Many experts recommend that antenatal testing begin at 32 weeks' gestation. Typical testing might include once- or twice-weekly fetal non-stress tests (NSTs) or modified biophysical profiles (Garrison 2015). The NST poses no harm to the fetus and involves the mother wearing one belt to measure fetal heart rate and another to monitor contractions over 20–30 minutes. A normal NST is "reactive," showing that the fetal heart rate accelerates during times of movement. A modified biophysical profile includes the NST, together with an assessment of amniotic fluid volume by ultrasonography. The modified biophysical profile is considered normal if the NST is reactive and there is at least one adequate pocket of amniotic fluid more than 2 cm deep.

Ultrasonography is another fetal assessment that can be used to identify the risk of macrosomia. Many obstetricians use ultrasonography at 36–39 weeks' gestation to assess fetal growth. However, ultrasonography is not a highly sensitive or specific method for identifying LGA infants, and clinical examination may be comparable. The ACOG guidelines recommend that clinicians assess fetal size late in the third trimester using either ultrasonography or clinical examination. In the future, as ultrasound technology continues to advance, ultrasonography may have a more defined role in the fetal assessment of women with GDM.

Obstetric Considerations

Given the potential risks of pregnancies complicated by GDM, timing and route of delivery are important considerations. Unlike in preexisting diabetes, well-controlled trials that examine the optimal timing of delivery in GDM are not available, and evidence-based recommendations cannot therefore be made. The ACOG guidelines suggest that expectant management should be practiced in women with GDM controlled with diet or drug therapy and recommend against delivery before 39 weeks' gestation (ACOG 2013). If glycemic control is poor or other maternal or fetal complications are present, an earlier delivery can be considered. The NICE guideline offers a similar recommendation, suggesting that women with GDM should be advised to give birth before the end of the 40th week of gestation, and elective delivery before this time can be considered in the presence of maternal or fetal complications (NICE 2015). In clinical practice, many obstetricians offer induction of labor for women with GDM at 39–40 weeks' gestation, or at the estimated date of delivery (40 weeks). Because the risk of shoulder dystocia is higher in pregnancies complicated by diabetes, ACOG also suggests that women with GDM with a predicted fetal weight of 4500 g or more be counseled about cesarean delivery as an option to reduce the incidence of birth trauma (ACOG 2013).

Intrapartum Glucose Control

Maternal hyperglycemia during labor and delivery can contribute to the risk of neonatal hypoglycemia (Blumer 2013). Thus, prevention of neonatal hypoglycemia is a primary goal of intrapartum glucose management. Hypoglycemia in the mother should be avoided if a long-acting insulin is used during labor (Cheng 2008a).

Of note, insulin requirements are usually decreased during labor because the woman is typically fasting, and the work of labor requires energy expenditure. Therefore, for women with GDM managed with insulin, it may be reasonable to omit the dose of long-acting insulin or give only one-half of the usual dose on the day of delivery (Garrison 2015; Cheng 2008a).

Both the Endocrine Society and NICE guidelines recommend a target plasma glucose concentration of 72–126 mg/dL during labor and delivery, whereas ACOG recommends a target of 70–110 mg/dL (ACOG 2005). Plasma glucose values should be monitored every 1–2 hours, and intravenous dextrose or insulin infusion should be administered as needed to maintain intrapartum glucose concentrations in the desired range (Blumer 2013). Women with diet-controlled GDM are unlikely to require intrapartum administration of insulin. Glucose concentrations in most women with GDM return to near-normal concentrations shortly after delivery, and glucose-lowering therapies should be discontinued immediately after birth (NICE 2015).

POSTPARTUM MANAGEMENT

Postpartum Screening

Within 24–72 hours of delivery and before returning to community care, women should have a glucose assessment (fasting plasma glucose or self-monitored glucose) to

exclude ongoing hyperglycemia (NICE 2015; Blumer 2013). Because women with a history of GDM are at a greater risk of developing prediabetes or type 2 diabetes, most guidelines recommend screening at 6–12 weeks postpartum using the one-step approach (2-hour 75-g OGTT) previously described (ADA 2016b; ACOG 2013; Blumer 2013). The NICE guideline differs, advocating screening with fasting blood glucose rather than the 2-hour 75-g OGTT, and advises against the routine use of the OGTT (NICE 2015). Studies evaluating the use of A1C, with or without fasting glucose, to diagnose postpartum glucose intolerance have not had consistent results with respect to its sensitivity, and, at least initially, A1C may still be affected by the increased RBC turnover during pregnancy (ADA 2016b; Benhalima 2015).

After the initial postpartum screening, some sources recommend continued use of the 2-hour 75-g OGTT, whereas others, such as the ADA, indicate that A1C, fasting glucose, or the 2-hour 75-g OGTT may be used. Nonpregnant thresholds should be used when doing postpartum screening. Screening should be repeated every 1–3 years and continued lifelong. The frequency of screening may depend on other risk factors for GDM or plans for subsequent pregnancies (ADA 2016b). Patients with identified glucose intolerance should be referred for treatment.

Data from the Nurses' Health Study II showed that the risk of developing diabetes in women with a history of GDM was 40% lower in those who followed healthy eating patterns (ADA 2016b). Furthermore, both metformin and intensive lifestyle intervention prevent or delay progression to diabetes in women with glucose intolerance and a history of GDM (ADA 2016b). Metformin reduced progression by 40%, whereas lifestyle intervention provided a 35% reduction (Aroda 2015). Thus, women with a history of GDM who are identified with glucose intolerance should be referred for preventive therapy.

Patient Counseling

As stated earlier, women with a history of GDM should be counseled on lifestyle modifications that support weight loss after delivery and reduce the future risk of metabolic syndrome and type 2 diabetes. These patients should also be informed of the importance of repeated screening for glucose intolerance, particularly before considering another pregnancy. The need for contraception should be emphasized to reduce the incidence of unplanned pregnancy. The choice of contraceptive should not be influenced by the history of GDM, but should be based on other medical conditions or contraindications present in the patient. Any contraceptive that is appropriate, given the concomitant medical conditions of the patient, can be considered. In addition, women with a history of GDM should be encouraged to breastfeed because this can assist with weight loss in the postpartum period and may reduce the risk of progression to type 2 diabetes later in life (Garrison 2015; Blumer 2013).

CONCLUSION

Optimal glucose control is key to reducing the risk of maternal and fetal complications in GDM. Most women with GDM can achieve adequate glucose control with nutritional therapy. For patients who do not achieve glycemic control with diet, drug therapy with insulin, metformin, or glyburide is

Practice Points

- **Glycemic targets for GDM are more stringent than for other types of diabetes mellitus and include fasting glucose of 95 mg/dL or less, 1-hour postprandial glucose of 140 mg/dL or less, and 2-hour postprandial glucose of 120 mg/dL or less.**
- **Most women with GDM can achieve glycemic targets with lifestyle modification.**
- **Nutritional therapy for women with GDM should emphasize distribution of calories (33%–40% carbohydrates, 20% protein, and 40% fat), with a focus on restriction of carbohydrates as needed to control glucose.**
- **Nutritional therapy for women with GDM should provide enough caloric intake to promote adequate weight gain. Suggested weight gain and caloric intake during pregnancy is based on pre-pregnancy BMI.**
- **Most women with GDM should engage in moderate exercise for 30 minutes most days of the week.**
- **There is no consensus on when to initiate drug therapy in GDM. In general, therapy should be considered when most glucose values in 1 week exceed glycemic targets. Clinicians should consider the severity and frequency of hyperglycemia, fetal growth, and patient factors when deciding to initiate pharmacotherapy.**
- **ACOG recommends metformin as an appropriate first-line therapy for GDM. NICE also recommends metformin as first-line therapy if the fasting glucose is less than 126 mg/dL at diagnosis.**
- **Women with GDM treated with metformin are more likely to require supplemental insulin than those treated with glyburide.**
- **Glyburide crosses the placenta to a minimal extent. Treatment of GDM with glyburide may be associated with a higher rate of fetal macrosomia and neonatal hypoglycemia.**
- **Glyburide is an appropriate therapy in GDM, especially if intolerance to metformin or refusal of insulin therapy is present.**
- **Insulin is listed as a preferred therapy in all the GDM-related guidelines and should be the agent of choice for women with marked hyperglycemia.**
- **Insulin aspart and insulin lispro are preferred insulins for the management of postprandial glucose. To date, insulin glulisine does not have human data in pregnancy.**
- **Both NPH insulin and insulin detemir are recommended as preferred basal insulins in GDM treatment. Randomized controlled trials with insulin glargine in GDM are lacking.**
- **Women with a history of GDM are at increased risk of type 2 diabetes later in life. They should be screened at 6–12 weeks postpartum and then every 1–3 years. Women who develop glucose intolerance should be referred for treatment.**

indicated. Although most women revert to nondiabetic status after delivery, a significant proportion of women with a history of GDM later develop prediabetes or type 2 diabetes. Pharmacists can play an integral role in GDM management by emphasizing the importance of prenatal care and screening for GDM, educating patients on the risks and benefits of various glucose-lowering agents for GDM, and providing evidence-based and patient-centered recommendations for lifestyle modifications and drug therapy in GDM management. In addition, pharmacists are in a key position to provide counseling on the importance of monitoring and techniques for monitoring the signs and symptoms of hypoglycemia, management of hypoglycemia, and methods to reduce the development of type 2 diabetes in the future.

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Self-Assessment Questions

1. A 39-year-old white woman (height 65 inches, weight 56 kg) has a medical history of asthma and seasonal allergies. Her family history is significant for hyperlipidemia and hypertension. Her current drug therapy includes budesonide MDI, albuterol MDI, and loratadine. Which one of the following best represents a risk factor for gestational diabetes mellitus (GDM) in this patient?

   A. Age
   B. Race
   C. Family history of hyperlipidemia
   D. BMI 20.5 kg/m^2

Questions 2 and 3 pertain to the following case.

The HAPO study was a landmark study to clarify the risks of gestational diabetes and maternal and fetal outcomes. Secondary outcomes included premature delivery, shoulder dystocia, intensive neonatal care, hyperbilirubinemia, and preeclampsia. The following data summarize the association between secondary outcomes and increasing maternal fasting glucose.

	Odds Ratio (95% CI)
Premature delivery	1.05 (0.99–1.11)
Shoulder dystocia	1.18 (1.04–1.33)
Intensive neonatal care	0.99 (0.94–1.05)
Hyperbilirubinemia	1.00 (0.95–1.05)
Preeclampsia	1.21 (1.13–1.29)

2. Which one of the following best summarizes the primary outcome of the HAPO study?

   A. Elevated maternal glucose was associated with higher rates of cesarean section delivery and infant birth weights greater than 90th percentile but unchanged rates of neonatal hypoglycemia and cord C-peptide greater than 90th percentile.
   B. Elevated maternal glucose was associated with higher infant birth weights greater than 90th percentile, neonatal hypoglycemia, and cord C-peptide greater than 90th percentile but unchanged rates of cesarean section delivery.
   C. Elevated maternal glucose was associated with higher rates of cesarean section delivery, infant birth weights greater than 90th percentile, neonatal hypoglycemia, and cord C-peptide greater than 90th percentile.
   D. Elevated maternal glucose was associated with lower rates of cesarean section delivery but higher rates of infant birth weights greater than 90th percentile, neonatal hypoglycemia, and cord C-peptide greater than 90th percentile.

3. Which one of the following best describes the association between increasing maternal fasting glucose and secondary outcomes in the HAPO study?

   A. Increasing fasting glucose was associated with a significant increase in all secondary outcomes, except with no significant effect on intensive neonatal care.
   B. Increasing fasting glucose was associated with a significant increase in shoulder dystocia and preeclampsia and no significant effect on the other secondary outcomes.
   C. Increasing fasting glucose was associated with a significant decrease in intensive neonatal care but a significant increase in all other secondary outcomes.
   D. Increasing fasting glucose was associated with a significant increase in shoulder dystocia, preeclampsia and premature delivery, and no significant effect on the other secondary outcomes.

4. For which one of the following patients (all with no history of GDM) would it be best to screen for diabetes at the first prenatal visit rather than waiting until 24–28 weeks' gestation?

   A. A 30-year-old African American woman with BMI 31 kg/m^2
   B. A 24-year-old Asian woman with BMI 20 kg/m^2
   C. A 34-year-old white woman with BMI 30 kg/m^2
   D. A 35-year-old Hispanic woman with BMI 23.5 kg/m^2

5. Which result will lead to diagnosis of GDM following the one-step approach with a 75-g oral glucose tolerance test (OGTT)?

   A. 1-hour glucose 160 mg/dL
   B. 1-hour glucose 175 mg/dL
   C. 2-hour glucose 150 mg/dL
   D. 2-hour glucose 160 mg/dL

6. A 30-year-old African American woman is at 24 weeks' gestation. Her physician is screening for GDM using the two-step approach, and her step 1 glucose was 160 mg/dL. She then continues to step 2 and has a 100-g OGTT. Using the NDDG criteria, which one of the following would most likely result in a GDM diagnosis?

   A. Fasting glucose 120 mg/dL, 1-hour glucose 180 mg/dL, 2-hour glucose 160 mg/dL, and 3-hour glucose 140 mg/dL

B. Fasting glucose 100 mg/dL, 1-hour glucose 180 mg/dL, 2-hour glucose 170 mg/dL, and 3-hour glucose 135 mg/dL
C. Fasting glucose 115 mg/dL, 1-hour glucose 185 mg/dL, 2-hour glucose 170 mg/dL, and 3-hour glucose 140 mg/dL
D. Fasting glucose 102 mg/dL, 1-hour glucose 178 mg/dL, 2-hour glucose 155 mg/dL, and 3-hour glucose 137 mg/dL

7. A 25-year-old pregnant woman at 28 weeks' gestation recently received a diagnosis of GDM. She has been monitoring her glucose, as instructed, and reports fasting glucose values of 82 and 86 mg/dL and postprandial values of 125 and 135 mg/dL. Which one of the following values best indicates suboptimal control of her glucose, according to the ACOG guidelines?

   A. Fasting glucose 82 mg/dL
   B. Fasting glucose 86 mg/dL
   C. 1-hour postprandial glucose 135 mg/dL
   D. 2-hour postprandial glucose 125 mg/dL

8. Which one of the following pairs of GDM complications is most likely to improve with treatment?

   A. Rate of infant macrosomia and maternal hypertensive disorders
   B. Rate of maternal hypertensive disorders and type 2 diabetes
   C. Rate of infant macrosomia and cesarean delivery
   D. Rate of infant shoulder dystocia and neonatal hypoglycemia

Questions 9–11 pertain to the following case.

H.B. is a 27-year-old woman (height 64 inches, current weight 70 kg [155 lb], pre-pregnancy weight 61 kg [135 lb]) at 28 weeks' gestation. She has just been given a diagnosis of GDM and is to begin lifestyle modification and glucose monitoring.

9. Which one of the following is best to recommend for lifestyle modification for H.B.?

   A. Consume a diet with no more than 20% of caloric intake from fat.
   B. Aim for a total caloric intake of 1600 mg per day.
   C. Eat three meals per day and avoid snacking in between.
   D. Engage in moderate exercise for about 30 minutes most days of the week.

10. Which one of the following is best to recommend for carbohydrate intake in H.B.?

   A. Choose carbohydrates with a low glycemic index, such as whole grains and fruits.
   B. Eat no more than 75 g of carbohydrates per day divided across meals and snacks.
   C. Consume most of the carbohydrate intake early in the day.
   D. Avoid evening snacks containing carbohydrates.

11. One week after starting nutritional therapy, H.B. returns to the clinic. She weighs 70 kg (155 lb), and her glucose values are as follows:

   Fasting: 95, 92, 89, 87, 94, 95
   One hour after breakfast: 150, 138, 154, 148
   One hour after lunch: 136, 126, 118
   Two hours after dinner: 112, 118, 108, 96

   H.B. reports that her typical meals include breakfast – two slices of white bread with peanut butter and apple, or cornflakes with milk and banana; lunch – salad with a glass of milk or iced tea; dinner – chicken or fish with vegetables and rice or couscous; and snacks – fruit, cheese, yogurt, pickles, and hummus and crackers. Which one of the following is best to recommend for H.B.?

   A. Reduce caloric intake to obtain better glycemic control.
   B. Reduce carbohydrate intake at breakfast.
   C. Increase carbohydrate intake with dinner.
   D. Increase carbohydrate intake to promote adequate weight gain.

12. If dietary modifications fail to provide adequate glucose control in GDM, which one of the following patients is the best candidate for metformin, according to the NICE guideline?

   A. 24-year-old with fasting glucose 120 mg/dL at diagnosis and history of GDM in a previous pregnancy
   B. 35-year-old with fasting glucose 137 mg/dL at diagnosis and history of polycystic ovary syndrome (PCOS)
   C. 26-year-old with fasting glucose 127 mg/dL at diagnosis and a multiple gestation pregnancy
   D. 38-year-old with fasting glucose 118 mg/dL at diagnosis and history of stage 3b chronic kidney disease

Questions 13 and 14 pertain to the following case.

F.F. is a 24-year-old woman at 28 weeks' gestation. She received a diagnosis of GDM 2 weeks ago (fasting glucose at diagnosis 110 mg/dL) and has begun nutritional therapy and moderate exercise. F.F.'s glucose values over the past week are as follows:

Fasting glucose (mg/dL): 96, 98, 101, 97, 106, 107, 92
One hour after breakfast: 147, 140, 135, 139
One hour after lunch: 142, 146, 138
Two hours after dinner: 120, 116, 136, 127

13. Which one of the following is best to recommend for GDM management in F.F.?

    A. Give acarbose.
    B. Give glyburide.
    C. Give metformin.
    D. Continue current lifestyle modification.

14. F.F. is concerned about taking drugs for GDM and wants more information on the risks of various medications to her unborn child. Which one of the following is the most important counseling point to provide to F.F.?

    A. Glyburide crosses the placenta to a greater extent than metformin.
    B. Metformin is associated with a greater risk of low blood glucose in the infant than glyburide.
    C. The long-term effects of fetal exposure to both metformin and glyburide are unknown.
    D. Women taking metformin are more likely to require the addition of insulin for GDM.

15. A 26-year-old woman at 30 weeks' gestation presents for a follow-up visit. Having received a diagnosis of GDM 2 weeks ago, she has implemented dietary modification. She has a medical history of PCOS. She reports GI intolerance to metformin, which was used to treat her PCOS, and states that she is afraid of injecting herself. Her glucose logs show an average fasting glucose of 99 mg/dL and averages of 128 mg/dL and 142 mg/dL 1 hour after breakfast and dinner, respectively. Which one of the following is best to recommend for GDM management in this patient?

    A. Give glyburide.
    B. Give metformin.
    C. Give insulin.
    D. Continue dietary modification and advise patient to avoid all carbohydrates.

16. A 33-year-old woman at 31 weeks' gestation (current pregnancy weight 86 kg [189 lb]) was given a diagnosis of GDM 3 weeks ago. Together with nutritional therapy, she has been taking metformin, and the dose has been titrated to 1000 mg twice daily. She is tolerating metformin well, but her glucose logs show moderate hyperglycemia after breakfast and dinner. Which one of the following is best to recommend adding to manage hyperglycemia in this patient?

    A. Glyburide 2.5 mg twice daily before breakfast and dinner
    B. 12 units of neutral protamine Hagedorn (NPH) insulin before breakfast
    C. 3 units of regular insulin before breakfast and dinner
    D. 4 units of insulin aspart before breakfast and dinner

17. A 32-year-old woman with GDM is at 30 weeks' gestation, and her current pregnancy weight is 80 kg (176 lb). She has marked hyperglycemia, and the physician would like to initiate intensive insulin therapy. Which one of the following is the best insulin regimen to recommend for this patient?

    A. 18 units of NPH insulin before breakfast and bedtime and 12 units of insulin aspart before breakfast, lunch, and dinner
    B. 20 units of NPH insulin before breakfast and dinner and 12 units of insulin lispro before breakfast, lunch, and dinner
    C. 36 units of insulin glargine at bedtime and 13 units of insulin glulisine before breakfast, lunch, and dinner
    D. 40 units of insulin detemir at bedtime and 13 units of insulin lispro before breakfast, lunch, and dinner

18. A 30-year-old woman delivered her first child 2 weeks ago. The patient was given a diagnosis of GDM during the pregnancy, and her glucose values returned to normal within 2 days of delivery. Which one of the following is best to recommend for her next diabetes screening, according to the ADA guidelines?

    A. Within the next week, she should have a 2-hour 75-g OGTT.
    B. In 4 weeks, she should have a 2-hour 75-g OGTT.
    C. In 8 weeks, she should have an A1C test.
    D. In 12 weeks, she should have a fasting glucose checked.

19. In a 10-year study, the Diabetes Prevention Program examined the effects of intensive lifestyle modification (ILS) and metformin on preventing diabetes in women with a history of gestational diabetes. Following are some results from the trial that highlight the effects of ILS or metformin on diabetes progression in women with prior GDM.

	Placebo	ILS	Metformin
Incidence of diabetes (cases per 100 person-years)	11.4	7.6	6.8
Reduction in incidence (compared with placebo)		35.2[a]	40.4[a]
Number needed to treat (to prevent one case in 10 years compared with placebo)		11.3	7.2

[a]p<0.05 compared with placebo.

Which one of the following best describes the results of the Diabetes Prevention Program?

A. Treatment with metformin was significantly more effective than ILS in reducing the progression to diabetes in women with a history of GDM.
B. Both metformin and ILS significantly reduced progression to diabetes compared with placebo in women with a history of GDM.
C. Metformin is associated with a 7.2% absolute risk reduction in progression to diabetes in women with a history of GDM.
D. Only one out of 11 women with a history of GDM will progress to diabetes if treated with ILS.

20. A 26-year-old woman had GDM during her recent pregnancy. At her 6-week postpartum visit, she has no signs of glucose intolerance. She would like to have another child in about 2 years but worries about the risk of GDM. Which one of the following is the most important counseling point to discuss with this patient?

A. Because your glucose is normal now, you have a very low risk of developing GDM with your next pregnancy.
B. ILS, together with breastfeeding, can help reduce your risk of developing type 2 diabetes later in life.
C. Taking metformin will reduce the risk of GDM with your next pregnancy by about 40%.
D. You should avoid using oral contraceptives to help reduce your risk of future GDM.

Learner Chapter Evaluation: Gestational Diabetes Mellitus.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Apply data regarding the risks of maternal hyperglycemia to the care of women with gestational diabetes mellitus (GDM).
13. Distinguish the differences between the various screening procedures for GDM.
14. Devise a monitoring plan to maximize maternal and fetal outcomes in patients with GDM.
15. Design an optimal treatment regimen, including nonpharmacologic and pharmacologic therapy, for GDM management.
16. Evaluate the role of oral hypoglycemic agents in GDM treatment.
17. Construct a plan for intra- and postpartum treatment of patients with GDM.
18. Please provide any specific comments relating to any perceptions of bias, promotion, or advertisement of commercial products.
19. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

New Pharmacotherapies for Type 2 Diabetes

By Charmaine D. Rochester-Eyeguokan, Pharm.D., BCPS, BCACP, CDE; and Roshni S. Patel, Pharm.D., BCPS

Reviewed by Christie A. Schumacher, Pharm.D., BCPS, BCACP, BC-ADM, CDE; and Judith L. Kristeller, Pharm.D., BCPS

LEARNING OBJECTIVES

1. Distinguish between the medication therapy recommendations in the updated 2016 diabetes clinical guidelines.
2. Evaluate the role of incretin-based therapies such as glucagon-like peptide-1 receptor agonists (GLP-1 RA) and dipeptidyl peptidase-4 (DPP-4) inhibitors and the sodium-glucose cotransporter-2 (SGLT-2) inhibitors for the treatment of type 2 diabetes.
3. Discuss the cardiovascular safety and efficacy of the DPP-4 inhibitors, GLP-1 RA, and SGLT-2 inhibitors.
4. Delineate the role and place in therapy of new insulin therapies in the treatment of type 2 diabetes.

ABBREVIATIONS IN THIS CHAPTER

ADA	American Diabetes Association
AACE/ACE	American Association of Clinical Endocrinologists/American College of Endocrinology
BG	Blood glucose
CKD	Chronic kidney disease
CV	Cardiovascular
DM	Diabetes
DPP-4	Dipeptidyl peptidase-4
ETD	Estimated treatment difference
GLP-1 RA	Glucagon-like peptide 1-receptor agonists
HF	Heart failure
SGLT-2	Sodium-glucose cotransporter-2
SU	Sulfonylurea
T2DM	Type 2 diabetes

Table of other common abbreviations.

INTRODUCTION

The number of U.S. adults with a diagnosis of diabetes (DM) has increased from 5.5 million to 29.1 million people (9.3% of the population) from 1980 to 2014 (CDC 2014a; CDC 2014b). This trend has also occurred worldwide. The WHO reported a similar increase from 108 million to 422 million over the same time period (WHO 2016). About 1.4 million Americans are given a diagnosis of DM each year, and in 2012, 86 million Americans age 20 and older had prediabetes (ADA 2016b). The total estimated cost of DM in 2012 was $245 billion, which includes $176 billion in direct medical costs and $69 billion in reduced productivity (ADA 2013).

Type 2 diabetes (T2DM) accounts for up to 90% of all DM cases, and the increase in prevalence over time has led to a surge in the development of new agents used to treat it. Currently, 12 classes of medications are approved for the treatment of T2DM: biguanides (metformin), sulfonylureas (SUs), meglitinides or glinides, thiazolidinediones or glitazones (TZDs), sodium-glucose cotransporter-2 (SGLT-2) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RA), dipeptidyl peptidase-4 (DPP-4) inhibitors, α-glucosidase inhibitors, dopamine-2 agonist (bromocriptine), bile acid sequestrants (colesevelam), amylin mimetics (pramlintide), and insulin (Appendix 2-1). Today's clinical pharmacists need to understand the differences between each medication class in order to make patient-specific therapeutic decisions. With pharmacists' expanding role, they are also responsible for reducing health care costs while addressing the psychosocial impact of DM on patients and the U.S. health care system. Other challenges facing pharmacists include reviewing updated clinical recommendations, assessing patients' glycemic control, setting glycemic goals, choosing therapeutic agents, improving medication adherence, and monitoring for adverse events and DM complications.

The complexity of proper T2DM self-care activities affects positive patient outcomes, thus requiring a disciplined patient to maintain long-term glycemic control. The patient should attain not only optimal glycemic targets, but also blood pressure and lipid goals. Although the optimal management of blood pressure, cholesterol, obesity, and lifestyle modifications is also critical in T2DM, this chapter focuses strictly on hyperglycemia management and how pharmacists can best recommend safe and effective treatment options.

CLINICAL GUIDELINE UPDATES IN DRUG THERAPY MANAGEMENT

The updated 2016 American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) guidelines continue to stress lifestyle modifications as a cornerstone for management, which should be initiated at diagnosis and continued throughout the life span of a person with DM. In both guidelines, metformin remains the preferred first-line therapy for most patients unless it is contraindicated or patients are intolerant of it (ADA 2016a; Garber 2016).

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the pathophysiology of T2DM
- Fasting and postprandial glycemic goals as defined by leading diabetes guidelines
- Knowledge of the pharmacologic agents used to treat T2DM
- Patient-centered approach to care

Table of common laboratory reference values

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm – 2016 executive summary. Endocr Pract 2016;22:84-113.
- American Diabetes Association. Standards of medical care in diabetes – 2016. Diabetes Care 2016a;39:S1-112.

ADA 2016 Guidelines

Many aspects must be considered when setting glycemic targets. The ADA proposes optimal A1C targets; however, each target must be individualized to the patient's needs and his or her disease factors (Table 2-1). It is recommended that glycemic targets consider life expectancy, duration of DM, presence of macro- or microvascular complications, comorbid conditions, risk of developing severe hypoglycemia, and a patient's social, psychological, and economic status. When possible, such decisions should be made with the patient, reflecting his or her preferences, needs, and values (AACE 2016; ADA 2016a). Both guidelines recommend A1C targets less than 6.5% for the healthy patient with low hypoglycemic risk and no concurrent illness. In general, the ADA-recommended goal A1C for most nonpregnant patients remains less than 7%, whereas that of the AACE/ACE is less than 6.5%. In both guidelines, glycemic targets are relaxed for children and older adults but are stricter for pregnant women (see Table 2-1).

In patients with newly diagnosed T2DM, clinicians should first initiate lifestyle modifications; however, when these efforts alone cannot achieve the glycemic targets, metformin monotherapy should be recommended. If the patient is contraindicated for, or intolerant of metformin, the clinician should initiate either a SU, TZD, DPP-4 inhibitor, SGLT-2 inhibitor, GLP-1 RA, or basal insulin, depending on the patient and the specific factors (Figure 2-1). The ADA guidelines recommend meglitinides as a substitute for SUs for patients who have erratic mealtimes resulting in late postprandial hypoglycemia. The α-glucosidase inhibitors colesevelam, bromocriptine, or pramlintide may be considered in specific situations, though they are not favorable because of modest efficacy, frequent administration, unwanted adverse effects, and limited clinical data supporting their use.

If patients receiving monotherapy do not achieve their target A1C after 3 months, the clinician should proceed to dual therapy. Initial dual combination therapy is also recommended for patients with T2DM who have an A1C of 9% or greater. Similarly, if patients receiving dual therapy do not achieve their target goals in 3 months, the clinician should proceed to triple therapy. Metformin forms the cornerstone of dual and triple combination therapies and has been widely studied with all classes of noninsulin antihyperglycemic therapies. Each new class of noninsulin agent added to the initial therapy lowers the A1C by around 0.9%–1.1%. The clinician should add either a GLP-1 RA or a basal insulin if the patient is not achieving the target A1C on oral triple combination therapy. If the patient's combination included GLP-1 RA, the clinician should add basal insulin to the regimen. Patients already receiving optimally titrated basal insulin should receive either GLP-1 RA or mealtime insulin to target their elevated postprandial blood glucose (BG). Clinicians should continue metformin in all patients and add a TZD or an SGLT-2 inhibitor if the patient appears refractory to insulin. A patient presenting

Table 2-1. ADA and AACE/ACE Goal A1C Targets for Different Patient Characteristics

Patient Description	ADA A1C Goals (%)	AACE A1C Goals (%)
ADA Recommendations – Healthy patients with: • Short duration of DM • Metformin therapy only • Lifestyle treatment only • No significant comorbidity • No significant cardiovascular disease • Long life expectancy AACE Recommendations – Healthy patients: • Without concurrent illness • With low hypoglycemic risk	< 6.5	6–6.5
Pregnant patients	< 7.5	≤ 6
Nonpregnant patients	< 7	≤ 6.5
All pediatric age groups	< 7.5	< 7.5[a]
Healthy older adults • Few coexisting chronic illnesses • Intact cognitive and functional status Rationale: Longer remaining life expectancy	< 7.5	7–8
Complex/intermediate older adults • Several coexisting chronic illnesses • 2-plus instrumental ADL impairments • Mild to moderate cognitive impairment Rationale: Intermediate remaining life expectancy; high treatment burden; hypoglycemia vulnerability; fall risk	< 8	7–8
Very complex/poor health older adults • Long-term care • End-stage chronic illnesses • Moderate to severe cognitive impairment • 2-plus ADL dependencies Rationale: Limited remaining life expectancy makes benefit uncertain	< 8.5	7–8

[a]Not specifically addressed but refers to recommendations by International Society for Pediatric and Adolescent Diabetes (ISPAD)/ International Diabetes Federation.

ADL = activities of daily living; DM = diabetes.

Information from: American Diabetes Association (ADA). Standards of medical care in diabetes – 2016. Diabetes Care 2016a;39:S11-S63; Garber AJ, Abrahamson MJ, Barzilay JI, et al. AACE/ACE - consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm – 2016 executive summary. Endocr Pract 2016;22:84-113; Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American Association of Clinical Endocrinologists and American College of Endocrinology – clinical practice guidelines for developing a diabetes mellitus comprehensive care plan. Endocr Pract 2015;21:1-87; and International Diabetes Federation 2011. Global IDF/ISPAD Guideline for Diabetes in Childhood and Adolescence.

with a BG of 300–350 mg/dL or an A1C of 10%–12% and symptoms of hyperglycemia (polyuria, nocturia, polydipsia, lethargy, polyphagia, weight loss) should immediately receive basal and mealtime insulin as the preferred combination.

A recommended treatment approach in choosing antihyperglycemic combination therapy is to select an agent that has shown beneficial effects in clinical trials and to target as many of the pathophysiologic defects of the disease as possible. These defects include decreased insulin secretion, increased glucagon secretion, insulin resistance, neurotransmitter dysfunction, and increased renal glucose absorption (Frias 2016). In addition, clinicians should choose agents that have either additive or synergistic effects that would achieve glycemic control with minimal hypoglycemia, nominal weight

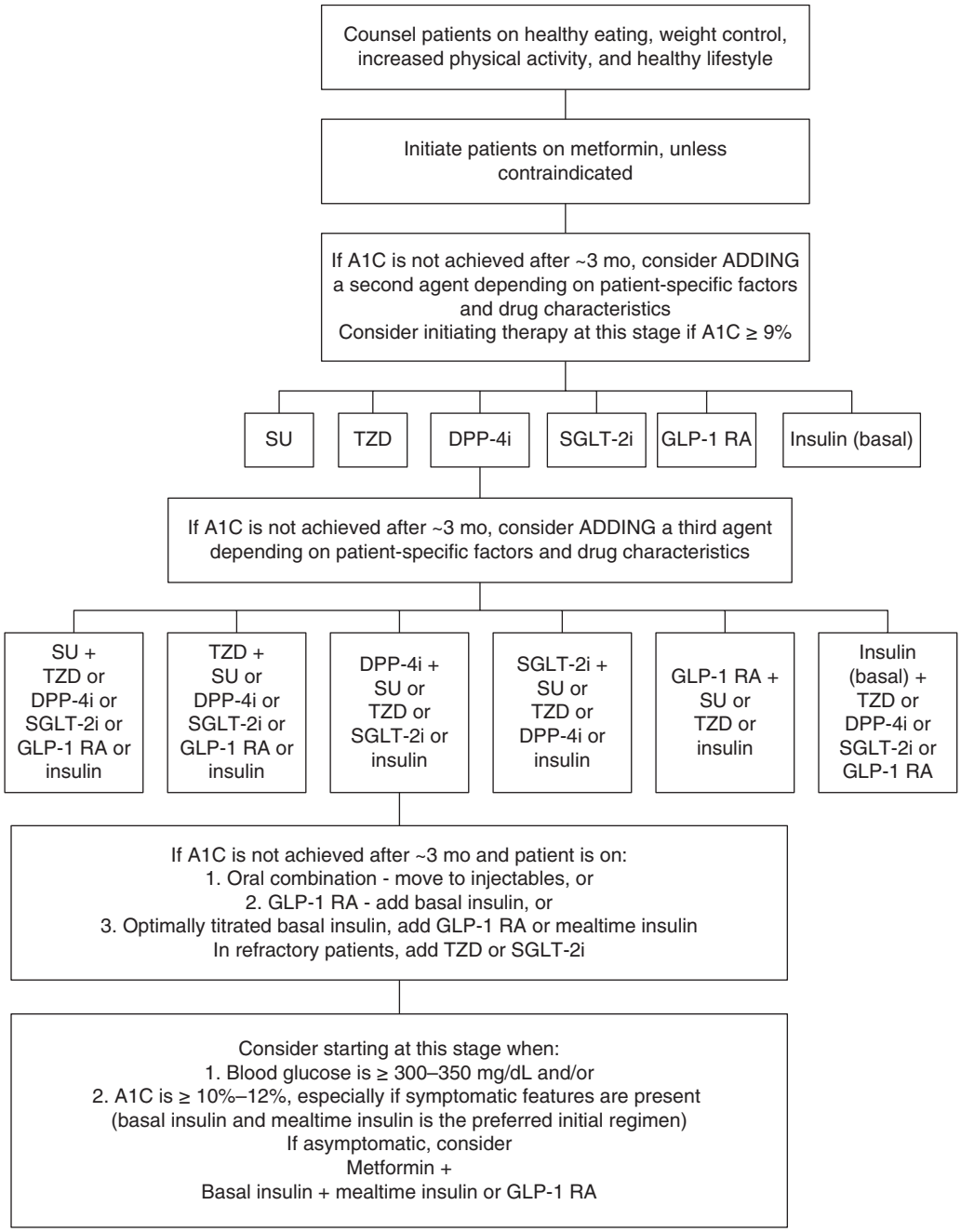

Figure 2-1. ADA antihyperglycemic therapy recommendations for patients with type 2 diabetes.

DPP-4i = dipeptidyl peptidase-4 inhibitors; GLP-1 RA = glucagon-like peptide-1 receptor agonists; SGLT-2i = sodium-glucose cotransporter-2 inhibitors; SU = sulfonylurea; TZD = thiazolidinedione.

Information from: American Diabetes Association (ADA). Standards of medical care in diabetes – 2016. Diabetes Care 2016a;39:S11-S63.

gain, or significant weight loss. Synergistic effects occur when the two agents given together achieve glycemic control more effectively than the sum of their separate effects using the same doses (e.g., SGLT-2 inhibitors and DPP-4 inhibitors). Additive effects occur when the effect of two agents taken together is equal to the sum of the effects of the two agents when taken separately (e.g., metformin and SU).

Researchers have evaluated several dual and triple combination therapies providing both additive and synergistic effects. For example, the dual combination of a DPP-4 inhibitor

and metformin provides a synergistic effect on metabolic control (Liu 2014). Metformin mainly improves glycemic control by reducing hepatic gluconeogenesis, whereas DPP-4 inhibitors prevent degradation of incretin hormones, thus improving pancreatic β-cell dysfunction. More recent studies show that metformin also increases GLP-1 secretion, suppresses DPP-4 activity, and up-regulates GLP-1 receptors in pancreatic β-cells, which improves insulin sensitivity (Liu 2014). Thus, the combination of a DPP-4 inhibitor and metformin provides better glycemic control than monotherapy in patients with T2DM. In contrast, combinations of DPP-4 inhibitors and GLP-1 RA are not recommended by either guideline because the combination is not well studied, and the theoretical benefits are limited. To date, no solid evidence supports this dual regimen, which acts on the incretin system.

The combination of an SGLT-2 inhibitor (empagliflozin) and a DPP-4 inhibitor (linagliptin) was recently approved as a single-tablet combination. Because the SGLT-2 inhibitors are not dependent on functioning β-cells or insulin action, the combination of DPP-4 inhibitors and SGLT-2 inhibitors has synergistic mechanisms, especially in patients with significantly deteriorated β-cell function and concerns for hypoglycemia. The combination was studied in patients with T2DM inadequately controlled on metformin with a baseline A1C of 8%–12% (DeFronzo 2015). Subjects were randomized to one of five treatment groups: a combination of empagliflozin 25 mg/linagliptin 5 mg, empagliflozin 10 mg/linagliptin 5 mg, and empagliflozin 25 mg, empagliflozin 10 mg, or linagliptin 5 mg as add-on therapy to metformin. The primary study end point was an A1C change in 24 weeks and sustained efficacy in 52 weeks. Study results show that the empagliflozin/linagliptin combination decreased A1C by –1.19% versus –1.08%, and –0.62%, –0.66%, and –0.7%, respectively ($p<0.001$ for all comparisons). The A1C goal of less than 7% by week 24 was attained in 61.8%, 57.8%, 32.6%, 28%, and 36.1% of subjects, respectively ($p<0.001$) and sustained efficacy to week 52. The safety profiles of the combination product were comparable with those of the established drugs individually. No major hypoglycemic events were reported. Combination therapy with a DPP-4 inhibitor, an SGLT-2 inhibitor, and metformin would be a reasonable approach for patients in whom hypoglycemia is a significant risk, such as patients with hypoglycemic unawareness, with inconsistent meal patterns, or prone to falls.

The combination of the oral SGLT-2 inhibitors and the injectable GLP-1 RA is not recommended in the ADA guidelines, possibly because of a lack of evidence of safety and efficacy at the time of publication. However, this recommendation may change with recent results from the DURATION-8 trial, the first clinical trial to combine an injectable GLP-1 RA and an oral SGLT-2 inhibitor as an addition to patients with T2DM inadequately controlled on metformin. The DURATION-8 trial was a 28-week, multicenter, double-blind, randomized, active-controlled, phase III trial of patients with an A1C of 8%–12% (Frias 2016). Patients were randomized to one of three treatment groups: once-weekly exenatide 2 mg subcutaneously plus once-daily dapagliflozin 10 mg orally, exenatide 2 mg subcutaneously with oral dapagliflozin-matched placebo, or dapagliflozin 10 mg orally with exenatide-matched placebo injections. The primary objective was to compare the efficacy and safety of the combination of exenatide and dapagliflozin with either exenatide or dapagliflozin alone. Results of the study show that the combination therapy was both additive and synergistic in its effect on glycemic control and cardiovascular (CV) end points and achieved its primary end point with the combination compared with exenatide or dapagliflozin. The combination therapy achieved an A1C of –2.0% versus –1.6% and –1.4%, respectively ($p<0.01$). More patients receiving the combination achieved the target A1C of less than 7% (45% vs. 27% and 19%, respectively) ($p<0.001$). Patients taking the combination therapy also had significantly greater weight reduction (–3.4 kg vs. –1.5 kg and –2.2 kg, respectively) ($p<0.01$), and significantly greater systolic blood pressure reduction (–4.2 mm Hg vs. –1.3 mm Hg and –1.8 mm Hg, respectively) ($p<0.05$). Rates of adverse events were similar between the treatment groups, and there were no significant hypoglycemic events. The most common adverse events occurring in more than 5% of all study groups were diarrhea, injection-site nodule, nausea, and urinary tract infection (UTI). We may expect to see this combination recommended in future DM guidelines if positive outcomes are also gleaned from the ongoing study of AWARD-10.

AACE/ACE 2016 Guidelines

The 2016 AACE/ACE DM guidelines continue to focus on A1C as the driving factor for therapeutic choices because initiation of therapy is based on A1C levels of less than 7.5%, 7.5% or greater, or greater than 9%. Unlike the ADA guidelines, the AACE/ACE guidelines recommend therapies in a specific order of hierarchy with drugs that have efficacy, safety, and weight-loss or weight-neutral effects. Similar to the ADA guidelines, the AACE/ACE guidelines recommend initiating metformin as monotherapy; however, if there is a contraindication or intolerance, the patient should be initiated on one of the following therapies in order of hierarchy: GLP-1 RA, SGLT-2 inhibitors, DPP-4 inhibitors, TZD, α-glucosidase inhibitor, SU/glinides, or basal insulin. Compared with the ADA guidelines, achievement of the A1C glycemic goals on monotherapy, dual therapy, or triple therapy is also evaluated after 3 months, and the patient is transitioned to the next step (Figure 2-2). Patients can also be initiated on dual therapy if they have an entry A1C greater than 7.5% and less than 9%. The dual therapies recommended in the hierarchy are metformin plus GLP-1 RA, DPP-4 inhibitors, and TZD, which are all agents with a low risk of hypoglycemia.

For patients presenting with symptoms of hyperglycemia and an A1C greater than 9%, the AACE/ACE guidelines recommend that insulin be initiated with or without other agents. However, it is recommended that asymptomatic patients be initiated on either dual or triple therapies (see Figure 2-2).

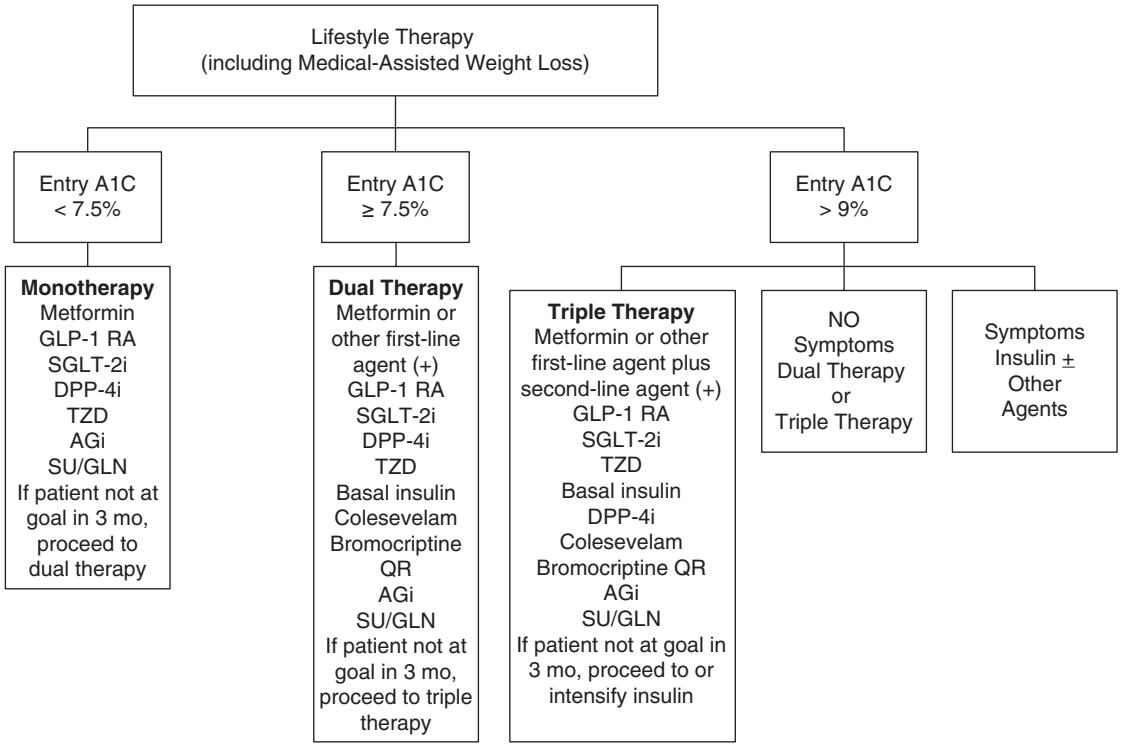

Figure 2-2. AACE/ACE guidelines for antihyperglycemic therapy recommendations for patients with type 2 diabetes.

A1C = Hemoglobin A1C; AGi = α-glucosidase inhibitor; DPP-4i = dipeptidyl peptidase-4 inhibitors; GLP-1 RA = glucagon-like peptide-1 receptor agonists; QR = quick release; SGLT-2i = sodium-glucose cotransporter-2 inhibitors; SU/GLN = sulfonylurea/glinides; TZD = thiazolidinedione.

Information from: Garber AJ, Abrahamson MJ, Barzilay JI, et al. AACE/ACE - consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm – 2016 executive summary. Endocr Pract 2016;22:84-113.

A PROPOSED CLASSIFICATION: THE EGREGIOUS ELEVEN

A new β-cell–centric model proposed by scientists challenges the existing diabetes diagnosis classification and treatment paradigm of the current guidelines (Schwartz 2016). The traditional classification does not reflect the current understanding of the underlying β-cell defect in patients with type 1 diabetes (T1DM), T2DM, and latent autoimmune diabetes of adults (LADA) and fails to clearly distinguish the ambiguity between these disorders. Significant overlap occurs also between typical patients presenting with DM. Some patients present with insulin resistance–associated T2DM but have features of T1DM, and some patients with T1DM present with obesity-related insulin resistance. There is also no clear consensus on the definition of LADA or whether it is a late manifestation of T1DM, T2DM with rapid destruction of β-cells, or a unique disorder on its own.

The β-cell–centric model assumes that the primary defect in all types of DM originates from an abnormal pancreatic β-cell as the core defect. The theory builds on the interaction between the genetically predisposed β-cells with factors leading to insulin resistance, environmental factors, immune dysregulation, and inflammation, which results in β-cell stress, dysfunction, or loss. The model is described as the "egregious eleven," in which six mechanisms contribute to β-cell dysfunction (liver, muscle, adipose tissue, brain, colon/biome, and immune dysregulation/inflammation), and five mechanisms are the result of β-cell dysfunction (defects in the β-cell, incretin, α-cell, stomach/small intestine, and the kidney). One advantage of the new classification is the identification of the mediating pathway of hyperglycemia, making therapy patient-centric and precise and enabling more targeted treatments for hyperglycemia. The primary goal of therapy is to prevent β-cell loss. Chosen therapies will improve β-cell function and reduce glucotoxicity, lipotoxicity, and insulin resistance by treating the inflammation and gut biome.

The proposal advocates introducing combination therapy early in disease management for its complementary actions and not as first-, second-, or third-line agents. If the primary defect is insulin resistance, the chosen therapy should be a combination of metformin and a TZD. Because incretins

target many different pathways, they are chosen for many of the defects such as an α-cell and β-cell defects. To target defects in the stomach or intestine, α-glucosidase inhibitors, GLP-1 RA, and pramlintide should be considered. Patients with increased appetite and lack of satiety will benefit from GLP-1 RA, whereas those with centrally controlled peripheral insulin resistance and sympathetic tone will benefit from bromocriptine quick release. The SGLT-2 inhibitors target the kidney, whereas probiotics, which can improve insulin resistance, β-cell function, and inflammation, may benefit the colon and biome. Therapies that target inflammation, immune dysregulation, and changes in the gut microbiome are an area for further research.

There are several guiding principles for clinicians who may consider embracing this model. Clinicians should treat as many of the egregious eleven targets as needed, with the least number of agents to obtain the lowest BG and A1C values possible, without undue weight gain or hypoglycemia. They should consider early combination therapy with agents that synergistically decrease CV risk factors and outcomes. Agents that address both fasting and postprandial BG and those that stabilize and preserve β-cells are preferred. Sulfonylureas and glinides should be avoided because they result in hypoglycemia, weight gain, increased CV risks, treatment failure, and β-cell failure. Insulin should be delayed in order to use agents that preserve β-cell function. Clinicians can also consider discontinuing insulin in patients who have residual β-cell function. When initiating basal insulin, clinicians should continue all other therapies, especially agents that decrease gluconeogenesis, delay gastric emptying, and have insulin-sparing effects. Clinicians are encouraged to match the right drug to the right patient according to patient comorbidities and drug tolerance. In this model, therapies for DM prevention are a consideration. Under this new construct, a physician has the option to use TZD, an SGLT-2 inhibitor, and incretin therapy in patients with T1DM (Schwartz 2016). If the β-cell–centric model is adopted by leading experts in DM, the current paradigm for DM classification, treatment, patient-specific therapy, and future research will shift.

PRACTICE GUIDELINES AND METFORMIN USE

Metformin is widely recommended as first-line therapy in all DM guidelines because it reduces myocardial infarction (MI) risk; reduces all-cause mortality; is cost-effective, safe, and efficacious with respect to glycemic control; has a low risk of hypoglycemia; and is weight-neutral compared with other agents. Despite these proven benefits, metformin was contraindicated in patients with kidney dysfunction, as suggested by serum creatinine concentrations at or above 1.5 mg/dL for men and 1.4 mg/dL for women or abnormal creatinine clearance. This year the ADA standards of care removed the serum creatinine cutoffs to opt for the estimated glomerular filtration rate (eGFR). For many years, metformin remained under-prescribed and underused in many patients with stable chronic kidney disease (CKD) who would have otherwise benefited from its CV and pleiotropic effects because of concerns for lactic acidosis (LA). Lactic acidosis more commonly occurred with phenformin, which was removed from the market, and had a mortality rate of 30%–50% with an incidence of 0.4–0.64 cases per 1000 patient-years (Sogame 2013). In comparison, metformin's incidence of LA is 0.03 cases per 1000 patient-years (10–20 times lower than with phenformin). Metformin has a wider therapeutic window, requiring higher blood concentrations than phenformin to cause LA. Moreover, metformin is generally believed not to cause an accumulation of lactate unless lactate metabolism is impaired for another reason (Gan 1992).

More recent studies show that elevated lactate concentrations were actually not caused by metformin. Moreover, metformin concentrations have not been shown to correlate with the severity of LA; hence, those with higher metformin concentrations do not have more severe LA, and metformin concentrations are not linked to mortality (Lipska 2011). Having T2DM by itself is a risk factor for LA, and more patients with T2DM have LA than does the general population. Metformin's use does not increase the risk compared with other antihyperglycemic agents. In addition, LA was extremely rare in patients treated with metformin compared with other agents after reviewing a Cochrane meta-analysis of pooled data from 347 comparative trials and cohort studies (Lipska 2011). The true incidence was 4.3 and 5.4 cases per 100,000 patient-years in the metformin and non-metformin groups, respectively, which was not statistically different.

Nevertheless, experts in the field around the globe differ in their opinions regarding the optimal definition of the safety of metformin use in patients with mild to moderate kidney disease. Experts recognize renal failure as a risk factor for adverse events with metformin use, and all recommend discontinuing metformin with an eGFR of less than 30 mL/minute/1.73 m^2. However, they differ with respect to recommendation on when to be cautious with use. The consensus statement issued by the ADA and the European Association for the Study of Diabetes reports that metformin is safe unless the eGFR drops below 30 mL/minute/1.73 m^2 in patients with mild to moderate but stable CKD (Inzucchi 2015a). In the UK, the National Institute for Health and Care Excellence recommends discontinuing metformin if serum creatinine exceeds 1.7 mg/dL or eGFR is less than 30 mL/minute/1.73 m^2. The current guidelines recommend reviewing the clinical circumstances when serum creatinine exceeds 1.5 mg/dL or eGFR falls below 45 mL/minute/1.73 m^2. However, these guidelines need to be updated because the European Medicines Agency recently concluded that metformin-containing agents can now be used safely in patients with moderate kidney function of eGFR 30–59 mL/minute//1.73 m^2 (EMA 2016). The Canadian Diabetes Association practice guidelines recommend

caution in patients with an eGFR less than 60 mL/minute/1.73 m^2, whereas the Australian Diabetes Society practice guidelines recommend caution with an eGFR of 30–45 mL/minute/1.73 m^2. In the United States, experts recommend metformin's use be initiated or continued with an eGFR less than 60 mL/minute/1.73 m^2 and the dose adjusted accordingly (Table 2-2). They suggest that the metformin dose be reviewed and reduced by 50% or to half-maximal in patients with an eGFR less than 45 mL/minute/1.73 m^2, and clinicians should not initiate metformin at this stage. Metformin should be discontinued once the eGFR falls to less than 30 mL/minute/1.73 m^2. Experts further recommend that clinicians be cautious in using metformin in patients with anticipated significant fluctuations in kidney status, other comorbidities, and albuminuria and in those taking concomitant potent diuretics or nephrotoxic agents (Lipska 2011).

Recently, the FDA requested a revision of metformin's medication labels to indicate its safe use in patients with mild to moderate renal impairment (FDA 2016b). The FDA also requested that the measurement of kidney function be changed from creatinine clearance to a glomerular filtration rate estimating equation (eGFR) because the latter more accurately considers a patient's age, sex, race, and weight. They suggest a baseline eGFR in all patients before starting metformin and an annual eGFR in all patients receiving metformin-containing therapies. Older adults and other patients at risk of renal impairment should have their renal function evaluated more often. Metformin is contraindicated in patients with an eGFR less than 30 mL/minute/1.73 m^2, and it is not recommended to initiate metformin in patients with an eGFR of 30–45 mL/minute/1.73 m^2. If a patient's eGFR falls below 45 mL/minute/1.73 m^2, the clinician should assess the benefits and risks of continuing metformin in that patient and discontinue the agent if the eGFR falls below 30 mL/minute/1.73 m^2. Clinicians should also discontinue metformin in patients before an iodinated contrast imaging procedure if their eGFR is 30–60 mL/minute/1.73 m^2; if they have liver disease, decompensated heart failure (HF), or abuse alcohol; and in those administered intra-arterial iodinated contrast. After the imaging procedure, metformin can be reinitiated in 48 hours, after reevaluation, if the renal function remains stable (FDA 2016b).

INCRETIN-BASED THERAPIES

On ingesting food, naturally occurring incretin hormones such as GLP-1 and glucose-dependent insulinotropic polypeptide are released from the small intestines into the circulation of healthy individuals. Incretin hormones are responsible for 50%–70% of insulin secretion after oral glucose administration (Garber 2011). The incretin effect results from the initiation of an insulin response by the incretin hormones that is greater with oral glucose than with parenterally administered glucose.

Endogenous GLP-1, with a half-life of only 1.5 minutes, is rapidly inactivated by DPP-4. As T2DM progresses, there is not only a decrease in the production of glucose-dependent insulinotropic polypeptide and GLP-1, but also a loss in the insulinotropic effects of glucose-dependent insulinotropic polypeptide and a poor response to the insulinotropic effects of GLP-1 leading to hyperglycemia (Holst 2011; Knop 2007). This is possibly because of impaired islet responses to the incretin hormones as an early sign of impaired glucose metabolism and insulin resistance. This occurs in patients with elevated A1C, poor insulin secretory reserve, and high BMI and in patients with obesity with an impaired response to carbohydrates. The effect is reversed when GLP-1, but not glucose-dependent insulinotropic polypeptide, is infused at a slightly supraphysiologic concentration because it improves insulin secretion and restores insulin response (Holst 2011; Knop 2007).

The incretin hormone GLP-1 has many physiologic effects that are attractive in T2DM management because it stimulates

Table 2-2. Recommendations for Metformin Use According to eGFR

Renal Dysfunction	eGFR (mL/min/1.73 m^2)	Maximum Daily Dose	Recommended Monitoring Parameters
None or mild	≥ 60	2550 or 2000 mg	Monitor renal function annually
Moderate	< 60 and ≥ 45	2000 mg	Monitor renal function every 3–6 months
Moderate	30–44	1000 mg	Lower dose by 50% or use half of the maximum dose. Monitor renal function every 3 mo. Do not initiate new patients on metformin. Continue if renal function drops to this level
Severe	< 30	Do not use	

eGFR = estimated glomerular filtration rate.

Information from: Lipska K, Bailey C, Inzucchi S. Use of metformin in the setting of mild-to-moderate renal insufficiency. Diabetes Care 2011;34:1431-7.

insulin secretion and inhibits glucagon secretion in a glucose-dependent manner, delays gastric emptying, and promotes satiety (Sheikh 2013). Two different classes of agents are available to address these benefits. First, the GLP-1 RA mimic the activity of naturally occurring GLP-1 and provide a supraphysiologic concentration of GLP that is about 6- to 10-fold higher than the physiologic concentrations in healthy individuals (Nauck 2009). Second, the DPP-4 inhibitors inhibit DPP-4, resulting in an increased endogenous concentration of GLP-1 that is 2- to 3-fold higher than the concentrations in healthy individuals. In comparison, GLP-1 RA have a greater A1C-lowering potential than DPP-4 inhibitors and a more pronounced effect on gastric emptying, satiety, and weight loss. Although the benefits are more pronounced than with the DPP-4 inhibitors, the GLP-1 RA also produce an increase in GI adverse effects. By contrast, the DPP-4 inhibitors produce a smaller A1C reduction, have minimal effects on gastric emptying, are weight-neutral, and have minimal adverse effects because of the lower amount of endogenous GLP-1 available (Nauck 2009).

GLP Receptor Agonists

Six GLP-1 RA are available for treating T2DM: exenatide, exenatide extended release, liraglutide, albiglutide, dulaglutide, and lixisenatide (Table 2-3). The long-acting GLP-1 RA

Table 2-3. Comparisons of Available GLP-1 RA

	Exenatide	Liraglutide	Exenatide Extended Release	Albiglutide	Dulaglutide	Lixisenatide
Dosage (subcutaneous administration)	5 mcg BID for 1 month; then 10 mcg BID as tolerated	0.6 mg once daily; increase weekly as tolerated up to 1.8 mg once daily	2 mg once weekly	30 mg once weekly; increase to 50 mg once weekly	0.75 mg once weekly; increase to 1.5 mg once weekly	10 mcg once daily for 14 days. Increase to 20 mcg once daily on day 15
Administration	Administer within 60 min before morning and evening meals	Administer any time of day without regard to meals[a]				Administer within the hour before the first meal of the day or the evening meal
Ease of administration	Prefilled pen	Prefilled pen	Pen with lyophilized powder that must be reconstituted	Pen with lyophilized powder that must be reconstituted	Prefilled pen for one time weekly use	Prefilled pen
Dosage adjustment with renal impairment (CrCl) Mild: > 50–80 mL/min/1.73 m^2 Moderate: 30–50 mL/min/1.73 m^2 Severe or ESRD: < 30 mL/min/1.73 m^2	No dosage adjustments for mild renal impairment Use with caution in moderate renal impairment Avoid in severe renal impairment	Adjustment not needed Use with caution in patients with renal impairment	No dosage adjustments for mild renal impairment Use with caution in moderate renal impairment Avoid in severe renal impairment	No dosage adjustment for mild, moderate, or severe renal impairment	No dosage adjustment for mild, moderate, or severe renal impairment, including ESRD	No dosage adjustment for mild or moderate renal impairment Avoid in severe renal impairment
A1C lowering (%)	–0.8 to 1.5	–1.1 to 1.6	–1.3 to 1.9	–0.78 to 1.55	–0.7 to 1.6	–0.7 to 0.9
Primary glycemic focus	Postprandial BG	Fasting and postprandial BG	Fasting BG	Fasting BG	Fasting BG	Postprandial BG

[a]For exenatide extended release, albiglutide, and dulaglutide, if patients miss a dose, they can administer it within 3 days. If > 3 days have elapsed, the patient should wait for the next scheduled dose.

BG = blood glucose; BID = twice daily; ESRD = end-stage renal disease.

Information from manufacturers' package inserts.

with half-lives of 12 hours to 5 days include exenatide extended release, albiglutide, liraglutide, and dulaglutide (Owens 2013). They rely on structural changes such as microsphere encapsulation, human albumin, or fatty acid side chains to delay their absorption and extend their duration of action. Except for liraglutide, which has once-daily dosing, all the long-acting agents have once-weekly administration. After a single dose, liraglutide forms heptamers and binds to albumin when injected subcutaneously, which delays its absorption and reaches a maximum concentration after 9–12 hours (Owens 2013).

Short-acting agents include exenatide and lixisenatide with half-lives of 2 and 2.8 hours, respectively. Although the short-acting agents result in a modest reduction in fasting BG, they have a stronger reduction in postprandial BG. For example, results of a study show that administering exenatide 5 and 10 mcg twice daily compared with placebo over 30 weeks only reduced fasting BG (–9 mg/dL and –10.8 mg/dL, respectively, vs. 14 mg/dL) ($p<0.0001$); however, postprandial BG was reduced by –52 mg/dL and –34 mg/dL, respectively, versus 0 mg/dL ($p<0.01$) (Kendall 2005).

The GLP-1 RA are injected subcutaneously into the abdomen, thigh, or upper arms. Except for a fixed dosage of exenatide extended release, the GLP-1 RA are initiated at a low dose and titrated weekly to the maintenance dosage (see Table 2-3). To reduce GI effects, short-acting agents are dosed within 60 minutes before meals, but longer-acting agents are dosed without regard to meals. Both exenatide formulations and lixisenatide should be avoided in severe renal impairment, and liraglutide should be used with caution. Both exenatide extended release and albiglutide require reconstitution before use. Albiglutide requires a 15- and 30-minute wait time to ensure proper reconstitution for the 30- and 50-mg pens, respectively. Exenatide extended release does not have a specific time to wait for reconstitution, but the pen requires mixing by tapping against the palm of the hand for more than 80 taps, and rotating the pen with every 10th tap. If it looks clumpy, it should be mixed again. If patients miss a dose of the weekly agents, they can administer it within 3 days. If more than 3 days have elapsed, patients should wait for the next scheduled dose.

The GLP-1 RA differ with respect to their A1C lowering and postprandial and fasting BG. Liraglutide lowers both fasting and postprandial BG, but postprandial lowering is greater than fasting (Flint 2011). Compared with placebo, liraglutide 1.2 and 1.8 mg lowered postprandial BG by 19.8 and 19.62 mg/dL ($p<0.001$), respectively, after 5 hours, and liraglutide 0.6, 1.2, and 1.8 mg decreased fasting BG by 13.3, 12.4, and 11.9 mg/dL ($p<0.001$), respectively (Flint 2011). The rationale for greater postprandial lowering is possibly explained by the modest reductions in the rate of gastric emptying and more significant effects on glucagon and insulin secretion.

No head-to-head trials have compared all GLP-1 RA with each other; however, one GLP-1 RA has been evaluated with another in several head-to-head trials. The randomized, open-label, parallel-group, placebo-control, noninferiority studies were designed to compare the safety and efficacy of the GLP-1 RA with respect to A1C lowering. Results of these studies show that the long-acting agents exenatide extended release, liraglutide, and dulaglutide at therapeutic dosages were superior to exenatide, with A1C lowering of –1.9%, –1.12%, and –1.51%, respectively, compared with –1.5%, –0.79%, and 0.99% for exenatide (Buse 2013; Buse 2009; Drucker 2008). However, lixisenatide was noninferior to exenatide (–0.79% vs. 0.96%, respectively) (Rosenstock 2013).

Liraglutide was also superior to exenatide extended release, with an A1C lowering of –1.48% compared with –1.28%, respectively (Wysham 2014). According to the evidence to date, none of the GLP-1 RA agents has been superior to liraglutide in A1C lowering in a head-to-head trial. In the AWARD-6 trial, dulaglutide 1.5 mg lowered A1C by –1.42% and liraglutide by –1.36% in a comparative trial, where dulaglutide was noninferior to liraglutide (Dungan 2014). Albiglutide was also noninferior to liraglutide (Pratley 2014).

Both long- and short-acting GLP-1 RA are associated with significant weight loss in patients with obesity and those with T2DM. Weight loss was associated with a reduction in total body fat, particularly trunk or visceral fat, which persisted while receiving therapy (Bloemendaal 2014). In a head-to-head study of liraglutide and exenatide, weight loss was comparable in both agents (–3.24 kg vs. 2.87 kg), but liraglutide was better tolerated (Buse 2009). When comparing liraglutide and dulaglutide, patients taking liraglutide had greater weight loss (–3.61 kg) than patients taking dulaglutide (–2.9 kg) ($p=0.011$) (Dungan 2014). Albiglutide and dulaglutide may not cross the blood-brain barrier to the same extent as exenatide and liraglutide, resulting in smaller effects on body weight (Lund 2014; Trujillo 2014). Therefore, liraglutide is a better choice if weight loss is a desired goal. Compared with patients who lose weight by dietary restrictions, the weight loss of GLP-1 RA was maintained in the long term while patients were receiving therapy. Once therapy is discontinued, patients will regain weight (Bunck 2011).

Liraglutide and dulaglutide appear to be equally effective in lowering A1C and fasting BG. Although liraglutide's benefits include its efficacy, weight loss, convenience of a prefilled pen, and no renal dose adjustment, its once-daily administration may be a barrier for some patients needing greater flexibility. Liraglutide is superior to dulaglutide with respect to weight loss; however, dulaglutide appears to be optimal for patients preferring once-weekly dosing and fewer injections. Albiglutide, though noninferior to liraglutide, is a less attractive once-weekly option because of the wait time for reconstitution of the lyophilized powder.

There are some differences in the adverse effects of the long- versus short-acting agents. For example, common adverse effects that occurred in 10% or more of patients taking exenatide extended release compared with exenatide

include nausea, vomiting, upper respiratory infection, injection-site bruising and subcutaneous nodule formation, whereas patients taking exenatide had more injection-site pruritus, diarrhea, constipation, and UTIs (Drucker 2008). Nausea is usually transient, peaking within 8 weeks of starting exenatide therapy, and typically resolves within 28 weeks. Conversely, for liraglutide, nausea peaks after 4–8 weeks of initiating liraglutide therapy and resolves after 8 weeks (Reid 2013). Patients can minimize the GI effects of short-acting agents by administering them within 60 minutes of a meal, titrating the dosage slowly for agents requiring titration, and avoiding high-fat or large meals. In addition, the GLP-1 RA should be avoided in patients with gastroparesis because of slowed gastric emptying, which can increase nausea (Reid 2013).

The incretin mimetics have been associated with C cell hyperplasia/medullary thyroid tumors in animals, but despite its boxed warning, it is unknown what the relevance is in humans. Therefore, the GLP-1 RA are contraindicated in patients with a personal or family history of medullary thyroid carcinoma. As a class, it has also been associated with acute pancreatitis requiring hospitalization and should be used with caution in patients with a history of pancreatitis (Singh 2013). A recent study confirmed that the GLP-1 RA had no increased risk of pancreatitis relative to SU use (Faillie 2014). Although the GLP RAs are associated with a low rate of hypoglycemia (0%–14.5% of patients in clinical trials), the risk of hypoglycemia increases when taken with insulin or insulin secretagogues; thus, lowering the dosage of insulin or insulin secretagogue is warranted (Garber 2011). Because patients taking GLP-1 RA with renal impairment have more nausea, clinicians should be cautious in initiating or escalating dosages (see Table 2-3). Despite these adverse effects, liraglutide has shown CV benefits in the LEADER trial in patients with high CV risk. This trial will be discussed later in the chapter. Despite the studies' strengths, one of the questions remaining is the applicability of CV benefit in patients with lower CV risks. Despite its benefits, clinicians should avoid liraglutide in patients with HF New York Heart Association classes III and IV, for whom the risks may outweigh the benefit, according to these findings (Margulies 2016).

In general, selection of a GLP-1 RA should be based on the frequency of administration, type of required glucose control (fasting or postprandial), adverse effects, patient-related variables, and patients' ability to use the administration devices. For patients who have a higher A1C and require improved fasting BG, long-acting agents such as exenatide extended release, liraglutide, dulaglutide, and albiglutide are better choices. For patients requiring improved postprandial blood glucose lowering, short-acting agents such as exenatide and lixisenatide are better choices. If both fasting and postprandial BG lowering and weight loss are required, liraglutide is optimal. The GLP-1 RA is an option for patients with frequent hypoglycemia and hypoglycemia unawareness because of their low risk of hypoglycemia. Weight loss with reduced appetite and increased satiety are added benefits (Reid 2013).

Most recently, lixisenatide was added to the U.S. market; however, it may enter a difficult market because comparative studies show that it was noninferior to exenatide in A1C lowering (Rosenstock 2013). In addition, according to the results of the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial, treatment with lixisenatide resulted in rates of major CV events, including HF and death from any cause, that were similar to placebo (Pfeffer 2015). With these neutral findings, though not causing harm, liraglutide still appears to be a better choice with respect to reduced CV risks (Marso 2016).

DPP-4 Inhibitors

Four DPP-4 inhibitors are available in the United States for the treatment of T2DM: sitagliptin, saxagliptin, linagliptin, and alogliptin.

The most notable differences in the pharmacokinetics among the DPP-4 inhibitors relate to their metabolism and elimination. The DPP-4 inhibitors at therapeutic dosages all reduce plasma DPP-4 activity by 70%–90% (Baetta 2011). The DPP-4 inhibitors are neither substrates, inhibitors, nor inducers of the CYP enzymes, except for saxagliptin, which is primarily metabolized by CYP3A4/5. Clinicians should use caution when coadministering saxagliptin with strong CYP3A/4 inhibitors (e.g., ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir), and the saxagliptin dose should be reduced to 2.5 mg once daily. Linagliptin is the only DPP-4 inhibitor primarily excreted by biliary excretion; however, all the other DPP-4 inhibitors are renally excreted and can be used in CKD at their recommended adjusted dose (Table 2-4) (Baetta 2011).

For trials lasting 24–26 weeks, monotherapy with DPP-4 inhibitors primarily reduced postprandial values more than fasting BG concentrations. For example, sitagliptin 100 mg reduced postprandial and fasting BG by 46.7 mg/dL and 17.1 mg/dL, respectively (Aschner 2006). A mean decrease in A1C noted in the DPP-4 inhibitor was 0.43%–0.61% from a baseline A1C of 8% (Del Prato 2011; Rosenstock 2009; DeFronzo 2008; Aschner 2006). As a class, the DPP-4 inhibitors have not been associated with appetite suppression or gastric emptying and therefore have a neutral effect on weight. Mean weight changes are generally less than 1 kg in drug-naive patients or those receiving combination therapy with metformin (Hinnen 2015). In general, the DPP-4 inhibitors have a low risk of hypoglycemia, with incidence rates of 1.3%–5.2%, compared with 0%–7.8% with placebo or active control in some studies (Barnett 2012; Aschner 2010; Rosenstock 2009; DeFronzo 2008). In one study evaluating linagliptin in older adult patients, hypoglycemia was reported by more patients taking linagliptin (24.1%) than by patients taking placebo (16.5%) because more patients were receiving

Table 2-4. Comparison of Available Dipeptidyl Peptidase-4 Inhibitors

	Sitagliptin	Saxagliptin	Linagliptin	Alogliptin
Dosage	25, 50, 100 mg/day	2.5, 5 mg/day	5 mg/day	6.25, 12.5, 25 mg/day
Elimination	87% urine	Renal and hepatic	Enterohepatic system 80% in the feces (5% in urine)	Renal 76%; fecal 13%
Dosage adjustment with renal impairment	CrCl ≥ 30–50 mL/min/1.73 m^2: 50 mg/day CrCl < 30 mL/min/1.73 m^2: 25 mg/day	CrCl ≤ 50 mL/min/1.73 m^2: 2.5 mg/day	Adjustment not needed	CrCl ≥ 30 to < 60 mL/min/1.73 m^2: 12.5 mg < 30 mL/min/1.73 m^2: 6.25 mg/day
Half-life (hour)	12.4	2.4 (3.1 active metabolite)	12	21
Adverse effect profile	Upper respiratory tract infection, UTI, headache, hypoglycemia (when taken with a sulfonylurea), acute renal failure, pancreatitis, and severe and disabling arthralgias			

Information from manufacturers' package inserts.

concomitant SUs (Barnett 2013). Patients taking linagliptin but not receiving SUs had similar rates of hypoglycemia (14.9% vs. 16.7%). Although there was no incidence of hypoglycemia in this study on concomitant insulin therapy, clinicians should still monitor patients for hypoglycemia on DPP-4 inhibitors and concomitant SUs or insulin.

In August 2015, the FDA issued a safety warning regarding the DPP-4 inhibitor class and severe joint pain (FDA Drug Safety 2016c). Cases of severe joint pain were identified through the FDA Adverse Event Reporting System (FAERS) database. In total, 33 cases of severe arthralgia were identified between October 16, 2006, and December 31, 2013, of which 22 resulted in symptoms within 1 month of initiating a DPP-4 inhibitor and 23 had symptom resolution in less than 1 month after drug discontinuation. Only 8 of the 33 cases had documentation of a positive rechallenge with a different DPP-4 inhibitor. Seven other case reports were found in the literature, two of which were also reported in the FAERS database. Symptom resolution occurred in six of the seven cases after drug discontinuation. In light of this information, the labeling of DPP-4 inhibitors has been changed to reflect the new warning.

In the past 5 years, three CV trials have been published regarding the safety and efficacy of DPP-4 inhibitors in CV disease. The SAVOR-TIMI 53 found an increased risk of HF hospitalizations, which was highest in the first year after patients started saxagliptin. Associated increased risks included a history of HF, high baseline brain natriuretic peptide (BNP) concentrations, and history of CKD. The EXAMINE trial also showed a trend toward more HF hospitalizations with alogliptin than with placebo. This prompted the FDA to issue a warning regarding the increased risk of HF with the use of saxagliptin and alogliptin, especially in people with preexisting heart or kidney disease. These trials are discussed later in the chapter.

Despite the efficacy of the DPP-4 inhibitors, there have been many debates, much controversy, and much conflicting data regarding the long-term safety of DPP-4 inhibitors in causing acute pancreatitis. Analysis from the FAERS in 2004–2009 showed that sitagliptin use increased the risk of acute pancreatitis more than 6-fold (6.74; 95% CI, 4.61–10) (Elashoff 2011). Observational studies have also been conflicting and inconclusive (Azoulay 2015). A large population-based case-control study using a Danish administrative database was evaluated to assess the association between incretins and hospitalized acute pancreatitis. Although the study results had an OR of 1.36 (95% CI, 1.08–1.69), the interpretation may be flawed because the other antihyperglycemic agents in the study had similar estimates (Azoulay 2015). The observation was driven more by having a diagnosis of T2DM itself than by the drug. Another observational analysis had limitations because it introduced significant confounders by introducing patients without T2DM, choosing few patients with T2DM, using a short duration of DPP-4 inhibitors, choosing patients with long-standing T2DM, choosing studies not limited to T2DM, and using a lack of appropriate comparators, and the studies were not conducted in patients with a history of pancreatitis. Clinicians should monitor patients closely after initiation or dose increase for symptoms of abdominal pain, nausea, vomiting, and elevated pancreatic enzymes

(serum lipase and/or amylase) more than 3 times the upper limit of normal. In addition, clinicians should monitor patients at high risk of alcohol and tobacco abuse and patients with a history of gallstones, high TG, and obesity, which also increases the risk. The DPP-4 inhibitors should not be initiated in any patient with a history of pancreatitis. If pancreatitis is suspected, the DPP-4 inhibitor should immediately be discontinued and not reinitiated.

The DPP-4 inhibitors have been also associated with upper respiratory infections, headache, nasopharyngitis, and UTIs occurring in more than 5% of patients. However, a meta-analysis shows the risks of adverse events and therapy discontinuation because these events were similar to placebo (Gooβen 2012).

Advantages of the DPP-4 inhibitors include safety, oral route, weight-neutrality, and once-daily administration. However, emerging adverse effects such as HF hospitalizations, acute pancreatitis, and severe joint pain may warrant increased vigilant patient monitoring.

SGLT-2 Inhibitors

Under normal physiologic conditions, 180 g of glucose is filtered daily by the renal glomeruli and then reabsorbed in the proximal convoluted tubule. This process is facilitated by sodium-glucose cotransporters (SGLTs), whereby they reabsorb 90% of glucose from the luminal membrane of the early proximal tubule, and SGLT-1 inhibitors absorb 10% of glucose from the late proximal tubule of the kidney (Kalra 2014). The kidney regulates BG by kidney gluconeogenesis, uses glucose from the circulation, and reabsorbs glucose from the glomerular filtrate. In the fasting state, 20%–25% of glucose is released into the circulation from kidney gluconeogenesis; however, in the postprandial state, the kidney releases about 60% of glucose. Patients with T2DM have increased rates of kidney gluconeogenesis in both the fasting and postprandial states and dysregulation of renal glucose homeostasis, giving rise to hyperglycemia (Nair 2010). By preventing the reabsorption of glucose and facilitating the urinary excretion of glucose in the proximal tubule independently of insulin secretion, the SLTT-2 inhibitors cause a decrease in BG with minimal hypoglycemia and may facilitate weight loss (Kalra 2014).

Three SGLT-2 inhibitors are available: canagliflozin, dapagliflozin, and empagliflozin (Table 2-5). Because SGLT-2 inhibitors are eliminated by the kidney, dosage adjustments are needed for renal impairment.

The SGLT-2 inhibitors lower A1C modestly by 0.5%–0.7% and decrease both fasting BG (–15 to –27 mg/dL) and postprandial BG (–48.6 mg/dL) (Stenlöf 2013; Weng 2013; Ferrannini 2010). With SGLT-2 inhibitors as a class, the net calorie daily loss is about 200–300 calories, leading to weight reductions of about 2–3 kg over 24–52 weeks (MacEwan 2012). The weight loss, which is mainly visceral fat, may be rapid initially, followed by a slower decline, and is associated with a decrease in waist circumference (Kalra 2014). Greater weight loss occurs in patients with long-standing DM and in those

Table 2-5. Comparison of Available SGLT-2 Inhibitors

	Canagliflozin	Dapagliflozin	Empagliflozin
Dosage	100, 300 mg daily	5, 10 mg	10, 25 mg
Administration	Take before the first meal of the day	Take in the morning without regard to food	
Dosage adjustment with renal impairment	eGFR > 60 mL/min/1.73 m^2: 100–300 mg daily eGFR 45–60 mL/min/1.73 m^2: 100 mg eGFR < 45 mL/min/1.73 m^2: Do not initiate therapy; discontinue therapy	eGFR > 60 mL/min/1.73 m^2: 5–10 mg daily eGFR < 60 mL/min/1.73 m^2: Do not initiate therapy; discontinue therapy	eGFR > 45 mL/min/1.73 m^2: 10–25 mg daily eGFR < 45 mL/min/1.73 m^2: Do not initiate therapy; discontinue therapy
Primary glycemic effect	Fasting and postprandial BG		
Adverse effect profile	Hypotension, hyperkalemia, ketoacidosis, bone fracture risk, decreased bone mineral density, increase in LDL, impairment in renal function, urosepsis, pyelonephritis, genital mycotic infections (balanitis, vulvovaginal candidiasis), foot and leg amputations		

SGLT-1 = sodium-glucose cotransporter-2.
Information from manufacturers' package inserts.

with a higher baseline weight. Weight loss can be sustained for up to 2 years and may be linked to reduced insulin dose requirements for patients with long-standing DM (Scheen 2014).

The blood pressure–lowering effects of the SGLT-2 inhibitors are independent of concomitant antihyperglycemic agents and occur without a compensatory increase in heart rate (Inzucchi 2015b). Blood pressure reduction is thought to occur because of osmotic diuresis initially and later because of inhibition of the renin-angiotensin-aldosterone system (RAAS). Weight reduction and sodium depletion also contribute to blood pressure lowering. In addition to these beneficial effects, empagliflozin decreases arterial stiffness, which may also play a role in decreasing blood pressure (Inzucchi 2015b). Patients treated with dapagliflozin 5 and 10 mg had small increases in HDL (6.5% and 5.5%) and LDL (0.6% and 2.7%) with small reductions in TG (–3.2% and –5.4%) (Inzucchi 2015b). Finally, the SGLT-2 inhibitors are also associated with a decrease in uric acid, which is associated with improvement in CV complications and HF. Despite the EMPA-REG OUTCOME trial, translation into long-term CV benefits from reduction in arterial stiffness, uric acid, lipid effects, and urinary albumin excretion remains to be clarified (Inzucchi 2015b).

Adverse effects that occurred in more than 10% in patients include hypotension, hyperkalemia, increase in LDL, acute kidney injury, genital mycotic infections including balanitis and vulvovaginal candidiasis, and hypoglycemia in combination with insulin/insulin secretagogues. In May 2015, the FDA issued a warning of diabetic ketoacidosis after identifying 73 cases associated with SGLT-2 inhibitors using the FAERS database between March 2013 and May 2015, all requiring ED visits or hospitalization (FDA 2016a). Of these cases, 44 were in patients with T2DM, 15 in patients with T1DM (off-label use), and 13 in patients with an unreported type of DM, and there was one case in a patient with LADA. The average BG in the reported cases was 250 mg/dL, which is much lower than in traditional diabetic ketoacidosis episodes. In addition, the FAERS database identified 19 cases of urosepsis between March 2013 and October 2014 resulting in hospitalization (FDA 2016a). Because of these findings, labeling changes were made to the Warnings and Precaution section for this class of agents. Despite these adverse effects, empagliflozin showed CV benefit in the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) study.

The positive outcomes from the EMPA-REG OUTCOME trial have generated significant speculations from the scientific community regarding the potential mechanisms. The trial showed curves for HF hospitalization, renal outcomes, and CV mortality that separated widely within 3 months of the start of the study and were maintained for more than 3 years (Mudaliar 2016; Ceriello 2015; Muskiet 2015; Zinman 2015). The typical CV benefits seen in the trial could not explain this separation such as improvement in glycemic control (A1C –0.4%), weight loss (–3%), decreased systolic blood pressure (–4 mm Hg), and reduction in uric acid (–6%) (Muskiet 2015). To explain the benefits seen, the study investigators propose potential vascular, neurohormonal, and cardiorenal effects and additional effects on hyperglycemia, weight, visceral adiposity, and blood pressure (Zinman 2015). Using the combination therapy of SGLT-2 inhibitors and angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), other researchers describe possible additive cardioprotective benefits on the vascular endothelium by activating the RAAS because many patients were receiving this combination therapy (Muskiet 2015). Still others postulate that the reduction observed in hospitalization for HF is partly explained by empagliflozin's ability to enhance myocardial function and regulate myocardial glucose uptake by increasing glucagon concentrations (Ceriello 2015). Although glucagon has been considered detrimental in DM, it has been proposed to play a key role in the regulation of myocardial glucose uptake and modulation of cardiac function. Glucagon has direct ionotropic and antiarrhythmic action, making it a possible consideration for HF therapy and the prevention of cardiovascular mortality.

More recently, another group of scientists proposed that empagliflozin improves myocardial fuel metabolism, myocardial contractility, and cardiac efficiency by shifting fuel use away from lipids and glucose toward ketone bodies, a "super fuel" (Mudaliar 2016). Ketone bodies, which are synthesized by the liver, have been useful in human survival during periods of starvation. Ketone bodies provide fat-derived calories to the brain, heart, kidneys, and other vital tissues much more efficiently than glucose or free fatty acids (FFAs). The heart is the highest consumer of ketone bodies. The SGLT-2 inhibitors increase ketone body production in patients with T2DM, and production is elevated in patients with HF. Insulin concentrations are also decreased in the fasting and postprandial state after SGLT-2 inhibitor therapy, which leads to an increase in lipolysis, FFA, and fat oxidation with higher ketone concentrations. In patients with T2DM and HF, a dysregulation of FFA oxidation and impaired glucose uptake and oxidation lead to myocardial dysfunction. In this setting, ketone bodies are the super fuel, which produces ATP more efficiently than glucose or FFA. Therefore, in the failing heart of a patient with T2DM, there is a metabolic advantage to effectively using ketone bodies as an alternative fuel.

These theories may partly explain the true mechanisms and need to be explored by research. Regardless of the benefits of empagliflozin, its adverse effects still need to be evaluated and weighed when choosing therapy. Before initiating SGLT-2 inhibitors in any patient with T2DM, the patient's volume status should be assessed for hypovolemia. This is especially true in those with renal impairment, those with low systolic blood pressure, older adults, and patients taking

diuretics because of the risk of hypotension. Even potential candidates for SGLT-2 inhibitors, such as younger patients with adequate renal function and stable blood pressure and volume status, need to be monitored for potential adverse effects (Rutecki 2014). Patients should also be monitored for hyperkalemia. Clinicians should evaluate the patient's profile for potassium-sparing agents (e.g., aldosterone, triamterene), potassium supplements, dietary salt substitutes, or ACEIs or ARBs to identify potential causes for the development of hyperkalemia. Clinicians should therefore discontinue potassium supplements or salt substitutes containing potassium. If potassium concentrations increase, consider whether to discontinue potassium-sparing agents, and continue to monitor potassium concentrations.

Although many adverse events have been reported, the EMPA-REG OUTCOME trial showed a significant reduction in CV outcomes. If the results of the EMPA-REG OUTCOME trial are replicated, SGLT-2 inhibitors may become more favorable in the guidelines. When patients are initiated on an SGLT-2 inhibitor, they should receive education regarding the signs and symptoms of possible euglycemic ketoacidosis, which usually include abdominal pain, shortness of breath, fatigue, nausea, and vomiting. Patients should be instructed to contact their physician's office immediately if they have these symptoms. Checking urine ketones is not recommended in the diagnosis of diabetic ketoacidosis secondary to SGLT-2 inhibitor use, and it is recommended that blood ketones (β-hydroxybutyrate) and arterial pH be checked to confirm the diagnosis. Consider any factor in a patient's history that may predispose the patient to ketoacidosis, including pancreatic insulin deficiency, bulimia or anorexia, prolonged fasting because of acute illness or surgery, and alcohol abuse. In these cases, consider discontinuing the SGLT-2 inhibitor.

In postmarketing surveillance, the FDA also reported bone fracture risk and decreased bone mineral density with canagliflozin (FDA 2016a). The increased risk of bone fracture occurred as early as 12 weeks after initiating therapy. Before initiating therapy, clinicians should consider the patient risk factors for bone fractures and, if possible, avoid the therapy in patients with osteopenia or osteoporosis because the risks outweigh the benefits. In addition, there is a new safety alert of a 2-fold risk of leg and foot amputations with canagliflozin (FDA 2016a). Patients should be educated to examine their feet regularly, practice proper foot care and hygiene, and report any new signs and symptoms of sores or ulcers. Other postmarketing complications include acute kidney injury, pyelonephritis, balanitis, and vulvovaginal candidiasis. Before initiating therapy, clinicians should consider all the factors that might predispose the patient to acute kidney injury such as hypovolemia, HF, chronic kidney insufficiency, and concomitant drugs (e.g., diuretics, ACEIs or ARBs, and NSAIDs). Clinicians should also discontinue the SGLT-2 inhibitor temporarily if the patient has reduced their oral intake as the result of acute illness, fasting, or fluid losses (e.g., GI illness or excess heat exposure).

UPDATES ON CV SAFETY T2DM

In 2008, the FDA provided guidance for manufacturers developing drug and therapeutic biologics for the treatment of DM. Specifically, recommendations were provided to show, using a minimum of 2 years of safety data from clinical studies, that new antihyperglycemic therapies did not carry an increase in CV risk using major adverse cardiac events (MACE) as a clinical endpoint. Although the individual outcomes used in the composite endpoint may vary from study to study, CV death, MI, and stroke should be included with or without other CV outcomes. Since 2008, the findings of several randomized controlled trials have been published (Table 2-6).

Saxagliptin

The SAVOR-TIMI 53 trial evaluated saxagliptin (Scirica 2013). The 16,492 patients either had a history or were at risk of CV events and were followed for 2.1 years. Overall, the trial found no difference between saxagliptin and placebo regarding the primary end point: a composite of CV death, nonfatal MI, or nonfatal stroke. For secondary end points, 3.5% of patients taking saxagliptin were hospitalized for HF compared with 2.8% of patients taking placebo (HR 1.27; 95% CI, 1.07–1.51; p=0.007). Therefore, this trial showed a 27% increase (0.7% absolute risk increase) in the risk of hospitalization associated with HF with saxagliptin use. The increased risk of HF hospitalization was highest in the first year after initiating saxagliptin, and those with a history of HF, high baseline BNP concentrations, and CKD were associated with highest risk.

Alogliptin

The EXAMINE trial evaluated alogliptin's CV risk profile using the same primary end point (White 2013). The 5380 patients had experienced either an acute MI or unstable angina requiring hospitalization before study entry. Alogliptin did not increase the risk of CV events compared with placebo. Other secondary CV end points were also similar, though HF hospitalization was not included as an outcome. A prespecified exploratory analysis then investigated hospitalizations associated with HF further, using a composite end point of first occurrence of all-cause mortality, nonfatal MI, nonfatal stroke, urgent revascularization as the result of unstable angina, and hospitalization for HF, which showed no difference between the groups (Zannand 2015). When the individual components of the composite end point were analyzed, hospital admissions for HF were similar between the arms (3.1% alogliptin vs. 2.9% placebo, p=0.657). A post hoc analysis also combined CV death and hospital admission for HF to make up another composite end point, which showed no

Table 2-6. Results of CV Outcome Trials for Patients with Type 2 Diabetes

Trial	No. of Patients	Characteristics of Patient Population	Active Group (vs. placebo)	Median Follow-up Time	Composite Primary End Point (Results)
SAVOR-TIMI 53	16,492	History of, at risk of, CV events	Saxagliptin	2.1 years	CV death, nonfatal MI, or nonfatal stroke (7.3% vs. 7.2%, NS)
EXAMINE	5380	Acute MI or unstable angina requiring hospitalization	Alogliptin	18 months	CV death, nonfatal MI, or nonfatal stroke (11.3% vs. 11.8%, NS)
TECOS	14,671	CV disease	Sitagliptin	3 years	CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina (11.4% vs. 11.6%, NS)
ELIXA	6068	MI or who had been hospitalized for unstable angina	Lixisenatide	25 months	CV death, MI, stroke, or hospitalization for unstable angina (13.4% vs. 13.2%, NS)
LEADER	9340	History of, or at risk of, CV disease	Liraglutide	3.8 years	CV death, nonfatal MI, or nonfatal stroke (13.0% vs. 14.9%, p=0.01 for superiority)
SUSTAIN-6	2735	History of, or at risk of, CV disease; or CKD	Semaglutide	2.1 years	CV death, nonfatal MI, or nonfatal stroke (6.6% vs. 8.9%, p=0.02 for superiority)
EMPA-REG OUTCOME	7020	CV disease	Empagliflozin	3.1 years	CV death, nonfatal MI, or nonfatal stroke 10.5% vs. 12.1%, p=0.04 for superiority)

CV = cardiovascular; NS = not significant; CKD = chronic kidney disease.

difference between alogliptin and placebo. Again, within this post hoc analysis, each component of the composite end point was examined, and HF-associated admissions were similar (3.9% alogliptin vs. 3.3% placebo, p=0.22) between the groups. It is unclear why the incidence of HF-associated admissions is not the same for the exploratory analysis (3.9%) and post hoc analysis (3.1%), given that the same patient population was analyzed. The lower incidence in the post hoc analysis could suggest that any CV death after HF was not counted as an HF-associated admission.

Sitagliptin

The Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes (TECOS) study evaluated sitagliptin's effects on CV outcomes using a primary composite end point of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina in 14,671 patients (Green 2015). After a median follow-up of 3 years, the composite primary end point was similar in the treatment groups (HR 0.98; 95% CI, 0.88–1.09). The secondary end point of HF-associated hospitalization had similar rates between the groups as well (HR 1.00; 95% CI, 0.83–1.20).

Summary of CV Safety of DPP-4 Inhibitors

Drawing conclusions from these trials on DPP-4 inhibitors can be challenging for several reasons. First, the sample size of the EXAMINE trial was much smaller than that for SAVOR-TIMI 53 or TECOS. The study populations differed with respect to DM duration, baseline A1C values, and previous HF. In addition, the studies had varied composite end points and methods for counting hospital admissions associated with HF, potentially leading to different interpretations. Although several meta-analyses have tried to address these issues, the data are largely driven by the results of the SAVOR-TIMI 53 trial and therefore have not been helpful in confirming or refuting the association (Son 2015). The FDA released a drug safety communication regarding the increased risk of HF specifically with saxagliptin and alogliptin, given the SAVOR-TIMI 53 and the EXAMINE data, respectively. Although both trials showed an increase in HF admissions, only the SAVOR-TIMI 53 trial showed a statistically significant difference. There is no FDA warning for sitagliptin, which may potentially be a safer alternative than either saxagliptin or alogliptin. Two additional trials, the VIVIDD and CAROLINA studies, will investigate the CV risk of vildagliptin and linagliptin, respectively.

Lixisenatide

The ELIXA trial was the first study to examine the CV safety of GLP-1 RAs (Pfeffer 2015). The patient population included individuals who recently had an MI or had been hospitalized for unstable angina. The primary end point was a composite of CV death, MI, stroke, or hospitalization for unstable

angina. The trial had a 2-fold design: to test for both the noninferiority and the superiority of lixisenatide to placebo. The primary end point was similar between groups (13.2% lixisenatide vs. 13.4% placebo; HR 1.02; 95% CI, 0.89–1.17). In addition, both HF and hospitalization for HF were similar between the lixisenatide and placebo arms, unlike some data on DPP-4 inhibitors.

Although superiority was not met, several factors must be considered. First, the median follow-up was 25 months. Many years may be required to identify a CV benefit in patients with T2DM as observed in the United Kingdom Prospective Diabetes Study (UKPDS) and Veterans Affairs Diabetes Trial (VADT) 10-year follow-up studies (Hayward 2015; Holman 2008). Second, patients in this trial had advanced CV disease with preexisting atherosclerosis.

Liraglutide

The LEADER trial investigated liraglutide's CV safety profile as well (Marso 2016). Like the ELIXA trial, the study design evaluated both superiority and noninferiority. Unlike in ELIXA, the 9340 patients in LEADER were followed for a median of 3.8 years, and the primary end point assessed the composite of first occurrence of CV death, nonfatal MI, or nonfatal stroke. Fewer patients in the liraglutide group had the primary end point compared with placebo (HR 0.87; 95% CI, 0.78–0.97; p<0.001 for noninferiority; p=0.01 for superiority; number needed to treat [NNT] = 66). When examining the individual components of the primary end point, all three occurred less often in the liraglutide group, but only death from CV causes was significant (HR 0.78; 95% CI, 0.66–0.93).

Semaglutide

The Semaglutide and Cardiovascular Outcomes in Patient with Type 2 Diabetes (SUSTAIN-6) trial evaluated the CV safety of semaglutide – a once weekly GLP-1 RA with an extended half-life (Marso 2016). Although this drug has not yet been approved for the treatment of T2DM by the FDA, the SUSTAIN-6 trial does offer additional insight on the CV outcomes associated with this class of agents. In the trial, 2,735 patients were followed for a median of 2.1 years. The primary composite endpoint was the first occurrence of death from CV causes, nonfatal MI, or nonfatal stroke. Similar to the LEADER trial, fewer patients in the semaglutide group experienced the primary end point compared with placebo (HR 0.74; 95% CI, 0.58–0.95; p<0.001 for noninferiority; p=0.02 for superiority; NNT=45). When examining the individual components of the primary end point, all three occurred less often in the semaglutide group, but only nonfatal stroke was significant (HR 0.61; 95% CI, 0.38–0.99). Although both the LEADER and SUSTAIN-6 trials showed similar findings in regards to the composite primary end point, the results for the LEADER trial were predominantly driven by death from CV causes, whereas the SUSTAIN-6 trial was driven by nonfatal stroke. Currently, other CV trials are underway that will continue to evaluate the CV safety of the GLP-1 RA class, including the EXSCEL for exenatide and REWIND for dulaglutide trials that may help to determine if a class effect truly exists.

Empagliflozin

Positive results also emerged from the EMPA-REG OUTCOME trial (Zinman 2015). In this study, a composite primary end point of death from CV causes, nonfatal MI, or nonfatal stroke was used. Among the 7020 patients, 10.5% in the empagliflozin arm had the primary end point compared with 12.1% in the placebo arm (HR 0.86; 95% CI, 0.74–0.99; p=0.04 for superiority; NNT=62). Death from CV causes drove the composite end point (HR 0.62; 95% CI, 0.49–0.77), and nonfatal MI and stroke showed no difference between the two groups. Several additional secondary end points favored empagliflozin, including death from any cause (5.7% vs 8.3%, p<0.001), hospitalization for HF (2.7% vs. 4.1%, p=0.002), and the composite of hospitalization for HF or death from CV causes excluding fatal stroke (5.7% vs. 8.5%, p<0.001). The CV trials for other agents, such as the CANVAS trial for canagliflozin and the DECLARE-TIMI 58 trial for dapagliflozin, will help determine whether the CV benefit observed with empagliflozin applies to the entire drug class.

Pioglitazone

More than a decade ago, the PROactive trial showed CV benefit with pioglitazone in a secondary end point (Dormandy 2005). In 5238 patients with T2DM and macrovascular disease, there was no statistically significant difference between those taking pioglitazone and those taking placebo for the primary composite outcome of all-cause mortality, nonfatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle. However, for the secondary outcome of a composite of all-cause mortality, nonfatal MI, and stroke, fewer patients reached this end point in the pioglitazone group than in the placebo group (11.6% vs. 13.6%, p=0.027). A second trial has now been published that adds evidence to that initial hypothesis-generating finding. Patients with ischemic stroke or transient ischemic stroke who did not have a diagnosis of T2DM but were considered insulin resistant (as determined by an assessment of β-cell function, fasting glucose, and insulin concentrations) were randomly assigned to receive either pioglitazone or placebo (Kernan 2016). After a mean follow-up of 4.8 years, the primary end point, fatal or nonfatal stroke or MI, occurred in 9% of patients in the pioglitazone group versus 11.8% of patients in the placebo group (HR 0.76; 95% CI, 0.62–0.93; p=0.007; NNT=36). These results are important because they suggest that pioglitazone has positive CV effects in patients who have insulin resistance but have not quite yet reached the level of hyperglycemia for a diagnosis of DM. Moreover, using an agent directed toward improving insulin resistance can translate to CV benefits.

SUMMARY

Results of these CV trials may have important implications. The effect of optimal glycemic control on microvascular risk reduction has been well established. Now, recent evidence supports a favorable effect of certain antihyperglycemic therapies on macrovascular risk. With new drugs showing some CV benefit, the choice of add-on therapy to metformin may become specific agents that have both CV safety and benefit rather than CV safety alone.

NEW INSULIN PRODUCTS FOR T2DM

Use of insulin effectively lowers BG in T2DM. Unfortunately, insulin is often underused because of inflexible dosing regimens, hypoglycemia, weight gain, and fear of injections. Newer insulin therapies have been introduced to address these barriers (Table 2-7).

Insulin Degludec

According to the package insert, insulin degludec is an ultra–long-acting basal insulin for patients 18 years or older and is available as both a U-100 and a U-200 formulation. When formulating insulin degludec, phenol and zinc are used to form a dihexamer solution. After subcutaneous injection and with the dispersion of phenol, the drug forms multihexamers, resulting in a depot that offers an extended release of the insulin (Vora 2015). The gradual release prevents the dosage from stacking (the buildup of insulin concentrations after repeated injections). Its half-life is about 25 hours, and the drug achieves steady-state concentrations within 3–4 days, with a duration of action of greater than 42 hours (Kalra 2015; Vora 2015). More than 99% of insulin degludec is strongly, although reversibly, bound to albumin. However, the concentration of this insulin is very low compared with albumin concentrations such that insulin degludec occupies less than 0.01% of albumin molecules. Therefore, insulin degludec's albumin binding potential results in only small clinical importance (Vora 2015). As such, there is no caution for use of insulin degludec in patients with low albumin concentrations. The prolonged duration of action for insulin degludec is different from that for insulin glargine, which uses pH-dependent crystallization for prolonged action, and different from that for insulin detemir, which uses albumin binding more prominently to achieve its prolonged duration.

Data from a large clinical trial program known as BEGIN involved more than 11,000 patients in various studies, using a "treat-to-target" design to investigate the safety and efficacy of insulin degludec (Vora 2015). In one of the BEGIN studies evaluating patients with T2DM who were insulin naive and taking metformin, insulin degludec was noninferior to insulin glargine. The A1C reductions after 52 weeks of therapy had an estimated treatment difference (ETD) of 0.09% (95% CI, –0.04 to 0.22%) (Zinman 2012). The percentages of patients in each arm achieving an A1C goal less than 7% were similar, although the fasting plasma glucose reduction was greater with insulin degludec than with insulin glargine (ETD of –0.43 mmol/L; 95% CI, –0.74 to –0.13). The incidence of overall hypoglycemia was similar between the two arms, though nocturnal hypoglycemia occurred less often in patients taking insulin degludec (0.25 vs. 0.39 events/patient-year of exposure, p=0.038). Mean insulin dosages and weight gain at the end of the trial were similar between the groups.

In a separate BEGIN trial, patients with uncontrolled T2DM already receiving insulin therapy with or without oral agents were randomized to receive either insulin degludec or insulin glargine in combination with insulin aspart with meals (Garber 2012). Results of this trial also showed the noninferiority of insulin degludec to insulin glargine with an ETD of 0.08% (95% CI, –0.05% to 0.21%). The proportions of patients achieving A1C goal, extent of fasting plasma glucose lowering, and mean daily insulin dosages were similar. The incidence of overall (11.1 vs. 13.6 episodes/patient-year of exposure, p=0.0359) and nocturnal (1.4 vs. 1.8 episodes/patient-year of exposure, p=0.0399) hypoglycemia was less common in the insulin degludec group.

A third BEGIN study specifically examined varying administration times of insulin degludec in patients with T2DM to determine the applicability of its ultra-long duration of

Table 2-7. Pharmacokinetic Properties of New Insulin Therapies

Product	Time to Onset of Effect	Time to Peak Plasma Concentration	Duration of Action (hours)
Insulin degludec	1 hour	9 hours	> 42 hours
70/30 insulin degludec/ insulin aspart	~14 minutes (aspart)	Varies per insulin component	> 24 hours (degludec)
Insulin glargine U-300	6 hours	12–16 hours	24 hours
Insulin lispro U-200	5–15 minutes	30–90 minutes	3–5 hours
Inhaled insulin	15–30 minutes	~53 min	3 hours

action (Meneghini 2013). Patients were randomized to one of three arms: insulin degludec flexible regimen (a prespecified rotation between morning and evening administration that allowed 8–40 hours between doses), insulin degludec given at the same time daily, and insulin glargine given at the same time daily. After 26 weeks, the flexible insulin degludec regimen was noninferior to both insulin degludec given at the same time daily and insulin glargine given at the same time daily with respect to A1C lowering. A similar proportion of patients within all three arms achieved an A1C goal of less than 7%. The fasting plasma glucose was reduced more with the flexible insulin degludec regimen than with insulin glargine (ETD –42 mmol/L; 95% CI, –0.82 to –0.02; p=0.04); the fasting plasma glucose lowering was similar between the two insulin degludec groups. Mean daily insulin dosages and weight gain were similar at the end of the trial. Overall and nocturnal hypoglycemia occurred at a similar rate in all three arms.

For patients with T2DM who have never received insulin, the recommended starting dose is 10 units once daily (Tresiba 2015 package insert). For patients already taking other long- or intermediate-acting insulin therapies, the same total daily unit dose can be used when changing from those therapies to insulin degludec. Although insulin degludec should be taken at the same time each day, there is some flexibility with the timing of administration, with a minimum of 8 hours between injections. The role of insulin degludec for BG control in patients with T2DM is its flexibility in the timing of administration and its potentially lower rate of nocturnal hypoglycemia, both of which offer an advantage over insulin glargine and insulin detemir.

70/30 Insulin Degludec/Insulin Aspart

Premixed insulins containing a fixed ratio of either rapid- or short-acting insulin with intermediate-acting insulin have been used as a potential approach for BG control, targeting both fasting and prandial values, particularly for patients with consistent meals and those who prefer fewer injections than the traditional basal-bolus approach, which can require up to 4 injections a day. The first combination product of basal insulin with a rapid-acting insulin has now been formulated. This product is composed of 70% insulin degludec and 30% insulin aspart. Insulin degludec aspart is effective in lowering BG in insulin-naive patients with T2DM taking metformin, with lower insulin dosages and lower rates of hypoglycemia than 70% insulin aspart protamine suspension and 30% insulin aspart injection [rDNA origin]), insulin analog (NovoLog Mix 70/30). Noninferiority was shown with A1C lowering (ETD of –0.03%) (95% CI, –0.18 to 0.13), with superiority in fasting plasma glucose lowering (ETD of –1.14 mmol/L) (95% CI, –1.53 to –0.76; p<0.001) (Fulcher 2014). The starting dose in insulin-naive patients is 10 units, which should be taken once daily with the largest meal. Patients must also use additional short- or rapid-acting insulin with other meals that are not timed with insulin degludec aspart. For patients already receiving insulin regimens, the same dosage can be used when changing to this product. Its advantage is that it reduces the basal-bolus concept from 4 injections to 3 injections daily, which is bleak at best. Rather, this product may be a favorable therapeutic option for patients who require basal insulin and prandial insulin with only one meal.

Concentrated Insulins

Some patients, such as those with severe insulin resistance, may require insulin dosages greater than 200 units daily. This requires insulin injections of over 1 mL (100 units of U-100) to be administered at the injection site, which can cause discomfort. Large insulin depots at subcutaneous injection sites also affect absorption (Reutrakul 2012). Current insulin syringes hold only 100 units, so patients requiring this increased insulin burden must use several injections for one dose, leading to poor adherence. Concentrated forms of insulin can address these issues.

U-500 regular insulin (Humulin R U-500) is 5 times more concentrated than U-100 insulin. Initially, this insulin was only available in a vial, leaving patients to use U-100 or tuberculin syringes, which required conversion to the corresponding syringe markings, leading to confusion and dosing errors. In 2016, a KwikPen product was introduced, which avoids the need for conversion. Other concentrated insulins have been introduced as well. Insulin degludec is now available as a U-200 formulation, which is bioequivalent to its U-100 counterpart. Insulin degludec U-200 is noninferior to insulin glargine in A1C lowering and superior in fasting plasma glucose lowering in patients with T2DM (Gough 2013). Both overall and nocturnal hypoglycemia as well as weight gain were similar between the arms. Insulin degludec U-200 is available as a FlexTouch pen device, which eliminates confusion because dosing conversions are not needed; it also allows 160 units to be injected at once.

A more concentrated insulin glargine became available after results from the EDITION clinical trial program were reviewed (Toujeo 2015 package insert). In patients with T2DM, insulin glargine U-300 provided similar BG control to insulin glargine U-100, but it is not bioequivalent (Riddle 2014). Of note, patients using U-300 required about 10 more units of basal insulin than patients treated with Lantus, which may warrant sooner patient follow-up for management (Riddle 2014). Nevertheless, the U-300 formulation had fewer episodes of hypoglycemia than the U-100 product. Insulin glargine U-300 is available as a SoloSTAR prefilled pen that has the number of units to be injected, also minimizing the risk of dosing errors. However, the pen allows only 80 units to be injected at once; therefore, for patients requiring higher insulin doses, more than 1 injection may be needed to administer a patient's dose, despite using this concentrated insulin.

The first concentrated mealtime insulin analog, insulin lispro human analog U-200 (Humalog U-200), is bioequivalent to Humalog U-100 in healthy patients (De la Pena 2016). No clinical trials are available for efficacy of the U-200 formulation in patients with T2DM. It is available as prefilled pen for injection, in which no dose conversions are needed.

Concentrated insulins provide the advantage of decreased volume per injection, fewer injections, and the need for patients to change their insulin pens less often. Their usefulness favors patients who require higher insulin burdens to achieve glycemic control, prompting better absorption and potentially improved adherence (Eby 2014). In addition, now that prefilled pens are available for all concentrated insulins, the risk of confusion and dosing errors has been reduced, allowing both patients and practitioners to feel more comfortable with these products.

Insulin Glargine (Basaglar)

At the end of 2015, a second insulin glargine (Basaglar) was approved; it has an amino acid sequence identical to

Patient Care Scenario

A 49-year-old man (weight 250 lb, height 70 in) has a medical history significant for T2DM, hypertension, heart failure with reduced ejection fraction (HFrEF), and dyslipidemia. He presents today for a follow-up visit for DM management. The patient checks his BG twice a day and brings his logbook today for review. Average fasting plasma glucose values over the past month include a fasting plasma glucose average of 180 mg/dL and a 2-hour postprandial dinner glucose average of 220 mg/dL. He states that he is adherent to his medication regimen and that he is tolerating it well.

His home drugs include metformin 1000 mg orally twice daily, lisinopril 40 mg orally daily, atorvastatin 40 mg orally daily, metoprolol succinate 100 mg orally daily, and furosemide 40 mg orally twice daily.

Vital signs today are blood pressure 138/90 mm Hg and heart rate 72 beats/minute. Laboratory test results/procedures (2 weeks ago) showed the following: A1C 8.1%, SCr 1.0 mg/dL, K 4.5 mEq/L, LDL 100 mg/dL, HDL 35 mg/dL, TG 180 mg/dL, TC 171 mg/dL, microalbumin - urine less than 20 mcg/mg, eGFR 65 mL/minute/1.73 m^2, and EF 40%.

What is best to recommend as the next step in managing this patient's T2DM?

ANSWER

Metformin therapy is appropriate, given that the patient is tolerating it well and his eGFR is greater than 60 mL/minute/1.73 m^2. However, because his A1C and self-monitoring BG values are elevated, an additional agent is warranted to achieve an A1C goal of less than 7%. The ADA provides several options for add-on therapy. Sulfonylureas, thiazolidinediones, DPP-4 inhibitors, GLP-1 RAs, SGLT-2 inhibitors, and basal insulin are potential options for consideration at this time, according to the ADA hyperglycemia treatment algorithm.

An SU is a potential but not optimal choice as add on therapy to metformin. Although an SU would lower his A1C to goal, could be taken orally, and is more affordable than other therapies, it can cause hypoglycemia and is associated with weight gain. Therefore, if possible, it should be avoided.

Thiazolidinediones, which have generic medication options like the SUs can be added on to metformin. However, a thiazolidinedione would not be an appropriate option at this time because it could cause fluid retention and exacerbate this patient's HF.

Use of DPP-4 inhibitors in HF has recently been controversial. The SAVOR-TIMI 53 trial showed that patients treated with saxagliptin had an increased risk of hospitalization from HF, and the EXAMINE trial showed a trend toward an increased risk with alogliptin. The TECOS trial did not show that sitagliptin offered CV benefit; however, it also did not show an increased risk of CV harm or hospitalizations related to HF, making it the safest choice in this class. Sitagliptin could be an option in this patient; however, cost and efficacy should be considered because its A1C-lowering potential might not get this patient to his goal of less than 7%.

A GLP-1 RA would be an appropriate choice at this time if the patient wished to use an injectable medication. Liraglutide would facilitate weight loss and reduce his A1C up to 1.5%. The LEADER trial showed that the NNT to prevent one CV event over 3 years is 66. The once-weekly agents may also be an option if the patient does not want a once-daily injection.

The EMPA-REG OUTCOME trial had significantly lower rates of death from CV causes, hospitalization for HF, and death from any cause with empagliflozin than with placebo. If empagliflozin were added to this patient's medication regimen, an A1C decrease of 0.5%–1% would be expected, which may not get this patient to goal. In addition, with his use of loop diuretics, the patient would need to be monitored closely for changes in volume status, dizziness, and hypotension.

Insulin therapy is the final potential option as add on therapy to metformin. However, since the patient's A1C goal can be achieved with other non-insulin therapies, it is not an optimal choice at this time, since it is associated with hypoglycemia and weight gain.

1. American Diabetes Association (ADA). Standards of medical care in diabetes – 2016. Diabetes Care 2016a;39(suppl 1):S11-S63.
2. Marso SP, Daniels GH, Brown-Frandsen KB, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311-22.
3. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28.

that of Lantus. Clinical trials have shown comparable efficacy with Basaglar and Lantus in patients with T2DM. In the ELEMENT 2 trial, Basaglar was noninferior to Lantus in reducing A1C in patients with T2DM after 24 weeks (Rosenstock 2015). The two products were similar with respect to the number of patients achieving A1C goals and adverse events, including hypoglycemia and weight changes.

Basaglar is the first "follow-on" (or "me-too") insulin with the potential to be marketed at a lower cost. As such, it could promote market competition between manufacturers and allow for more affordable medication costs for patients.

Technosphere Insulin

Alternative insulin administration routes have been investigated for some time because perceived barriers to subcutaneous insulin have resulted in patient reluctance. However, only inhalation routes have come to fruition in drug development. The first inhaled insulin product (i.e., Exubera) was released in 2006 and was available for only 1 year because of low patient and provider acceptance. In 2014, Technosphere insulin, with different pharmacokinetics and a more convenient delivery method, was introduced. Technosphere insulin is a dry powder regular human (recombinant DNA) insulin that uses the excipient fumaryl diketopiperazine to carry insulin particles within microspheres (Nuffer 2015). After inhalation, these particles dissolve immediately in the neutral pH environment of the lungs, leading to a quick onset with a duration of action of 3 hours. This requires the insulin to be administered relative to mealtimes. Finally, the bioavailability of Technosphere insulin is 21%–30% compared with regular subcutaneous insulin.

Clinical trials have investigated both the safety and the efficacy of the inhaled insulin in patients with T2DM (Nuffer 2015). Technosphere insulin with basal insulin was compared with a biphasic insulin aspart mixture and showed noninferiority. However, the extent of glucose-lowering potential of Technosphere insulin is less than that of other rapid-acting subcutaneous insulins. The most common adverse effect associated with inhaled insulin is cough. The rate of hypoglycemia in patients treated with Technosphere insulin was lower than in patients treated with an insulin comparator. In addition, decreases in forced expiratory volume in 1 second occurred within the first 3–6 months of use, which, although reversible with discontinuation, led to recommendations for spirometry and contraindications for use in both smokers and patients with chronic obstructive pulmonary disease.

Data have not shown an improved quality of life or better patient satisfaction with Technosphere insulin compared with subcutaneous insulin (Pittas 2015). Initial sales since it was introduced to the market have been low with this second non-needle insulin therapy (like Exubera). However, with a new marketing strategy set to take place, the product manufacturer continues to advocate for the use of Technosphere insulin.

CONCLUSION

Although metformin remains the first-line therapy, the selection of add-on therapy is evolving. Both patient- and drug-specific factors should be considered when selecting a therapy to achieve glycemic goals, prevent micro- and macrovascular complications, minimize adverse drug events, and increase patient satisfaction and quality of life. Incretin therapies offer the advantage of less hypoglycemia, given that they are glucose-dependent. Specifically, the GLP-1 RA can often result in additional weight loss, a beneficial characteristic to most patients with T2DM, whereas the DPP-4 inhibitors remain weight-neutral. Moreover, the efficacy of the GLP-1 RA has been significant in clinical trials, allowing patients to better achieve their glycemic targets than with other therapies, including insulin. The most common adverse drug event associated with this class is nausea, which may preclude its use in certain patients unable to tolerate the drug. A subcutaneous route of injection and cost may also preclude its use. The DPP-4 inhibitors are associated with an A1C reduction that may be less than with other drug classes; however, they are also tolerable, with few adverse drug events identified outside arthralgia. The SGLT-2 inhibitors offer a new mechanism of action for treating T2DM, independent of the pancreas as a drug target and with comparable efficacy with other oral antihyperglycemic agents. Although the incidence of hypoglycemia remains low with this class, unfavorable urogenital infections and the new concern for ketoacidosis may limit its usefulness in clinical practice. All three classes should follow renal dosing adjustments, when necessary, and monitoring for efficacy and safety should routinely occur according to guideline recommendations. Specifically, liraglutide and empagliflozin are the first of their classes to have CV benefit associated with their use.

A newly proposed β-cell–centric model challenges the existing DM classification and incorporates a more logical approach. The model will support best practice, if embraced, because it will identify the mediating hyperglycemia pathway operating in each patient and direct treatment to the patient's specific dysfunction.

Insulin therapy is still a viable option to help patients achieve their A1C goals. A variety of formulations and concentrations now exist that have tried to combat some of the barriers associated with insulin use. For instance, concentrated insulin allows less volume to be injected with each dose. The extended duration of action insulin, degludec, allows patient flexibility in the timing of administration each day. Finally, the first "follow-up" insulin, glargine, is now available, which has the potential to lower medication costs for patients. Although non-injectable routes have been extensively studied, none has succeeded in gaining momentum into routine prescribing practices. Despite this, with the continuously growing armamentarium of pharmacotherapies for T2DM, safety concerns are still present that warrant attention. Both the CV safety profile and the potential benefit should be considered when selecting therapeutic regimens.

Practice Points

Many challenges face the pharmacist in optimizing pharmacotherapy for patients with T2DM. As a result, updated guidelines, new therapeutic entities, and safety issues continue to evolve:

- **The 2016 ADA and AACE/ACE guidelines continue to advocate for metformin as first-line therapy and encourage clinicians to evaluate patient-specific factors in clinical decision-making. The β-cell–centric construct is a potential new model proposed for the classification and treatment of DM, which recognizes the abnormal β-cell as the primary defect in DM.**
- **The ELIXA trial, which evaluated the CV benefits of lixisenatide, a GLP-1 RA, in patients with T2DM and recent acute coronary syndrome, did not show a definitive CV benefit. However, the LEADER trial, which evaluated liraglutide in patients with at least one CV coexisting condition or CV risk factor, had fewer events in the primary composite outcome, CV death, and death from any cause than the placebo group.**
- **The DPP-4 inhibitors are a viable option to add to metformin as dual therapy; however, the TECOS trial, which evaluated sitagliptin and its effects on CV outcomes, did not show a definitive CV benefit. New data are still coming out regarding the DPP-4 inhibitors' increased risks of arthralgias.**
- **Empagliflozin, an SGLT-2 inhibitor, showed significant improvement in CV benefits in the EMPA-REG OUTCOME trial, which significantly decreased the primary composite end point of CV death, nonfatal stroke, and MI in patients with T2DM and high CV risk. These emerging data should be weighed against the potentially significant adverse effects, which include foot and toe amputations, yeast and UTIs, and euglycemic ketoacidosis.**
- **Insulin therapies provide significant BG lowering over oral drugs. New formulations have been developed to allow more flexible and convenient dosing regimens; however, hypoglycemia, weight gain, and costs remain concerns.**

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Self-Assessment Questions

21. A 75-year-old woman (height 64 inches; weight 82 kg; A1C 7.5%) received a diagnosis of type 2 diabetes (T2DM) 6 months ago. Her primary care physician recommended lifestyle modifications and initiated metformin 500 mg twice daily. Her medical history includes stage 4 stomach cancer (diagnosed 2 months ago), and she receives weekly chemotherapy. Today, her laboratory values show an estimated glomerular filtration rate (eGFR) of 29 mL/minute/1.73 m^2 (15% decline from 6 months ago). She says that her fasting blood glucose (BG) over the past 2–3 weeks was 130–160 mg/dL, with an average of 150 mg/dL. She also says that she is tolerating metformin well. She denies polyuria, polydipsia, polyphagia, nocturia, lethargy, weight loss, or tiredness. According to the 2016 AACE/ACE diabetes (DM) guidelines, which one of the following, in addition to lifestyle modifications, is the best treatment option for this patient?

    A. Continue current metformin therapy.
    B. Continue metformin and add exenatide extended release 2 mg once weekly.
    C. Discontinue metformin and initiate saxagliptin 2.5 mg daily.
    D. Discontinue metformin and initiate exenatide 5 mcg twice daily for 1 month; then titrate to 10 mcg twice daily as tolerated.

22. A 28-year-old man (height 71 inches; current weight 79 kg [175 lb]) received a diagnosis of T2DM 6 months ago. He was discontinued from metformin 1000 mg daily after complaints of severe diarrhea (5 loose stools daily) for 2 months after diagnosis. He is currently tolerating sitagliptin 100 mg daily and reports no adverse effects for 4 months. The patient is trying to closely follow dietary guidelines and is adherent to his monotherapy. He runs 4 miles daily. He has no other pertinent medical history. His A1C today is 7.3%. According to the ADA guidelines, which one of the following is best to recommend for this patient?

    A. Continue sitagliptin 100 mg daily.
    B. Add empagliflozin 10 mg daily.
    C. Change to alogliptin 25 mg daily.
    D. Reinitiate metformin at 500 mg twice daily.

23. A 27-year-old man (height 74 inches; weight 113 kg [250 lb]) was given a diagnosis of T2DM 7 months ago He states that he has been adherent to the combination of metformin 1000 mg twice daily and sitagliptin 100 mg daily for the past 4 months. He denies symptoms of polyuria, polyphagia, polydipsia, nocturia, or lethargy. He states that over the past 3 weeks, his fasting BG was 120–140 mg/dL and his 2-hour postprandial BG was 180–200 mg/dL. His A1C today is 8.4%; chemistries and liver function tests remain normal. He has no other medical conditions. He states that he is starting employment next week as an interstate commercial truck driver and will be on the road for long periods. According to the 2016 ADA guidelines, which one of the following, if added to his regimen, would best improve this patient's glycemic control?

    A. Albiglutide 30 mg once weekly and increase to 50 mg once weekly
    B. Empagliflozin 10 mg once daily
    C. Glipizide 5 mg once daily
    D. Insulin glargine 10 units every evening

24. A 58-year-old man (height 68 inches; weight 95 kg [210 lb]) is given a diagnosis of T2DM in the clinic today. He denies polyuria, polydipsia, nocturia, lethargy, weight loss, or tiredness. The patient endorses polyphagia and poor satiety. His fasting BG is 250–350 mg/dL; his A1C is 9.1%; and his renal function is normal. The primary care physician requests a consult from the clinical pharmacist. According to the proposed egregious eleven classification of DM, which one of the following is best to initiate for this patient?

    A. Glipizide extended release 5 mg once daily
    B. Sitagliptin 100 mg once daily
    C. Empagliflozin 10 mg once daily and glimepiride 2 mg daily
    D. Albiglutide 30 mg once weekly and metformin 500 mg daily

25. A 30-year-old woman (BMI 30 kg/m^2) with T2DM for 1 year presents to the clinic for a follow-up visit. Her A1C is 8.0%; fasting BG is 110–160 mg/dL; and 2-hour postprandial BG is 150–200 mg/dL). The patient states that she is adherent to lifestyle modifications, metformin 1000 mg twice daily, and empagliflozin 25 mg daily for the past 6 months. Her goals are better glycemic control and weight loss, and she desires an additional agent with proven cardiovascular (CV) benefits. She also states that she is busy and wants an agent with simple administration. She denies symptoms of hyperglycemia. Which one of the following would best to initiate to help this patient achieve her goals?

    A. Albiglutide
    B. Exenatide
    C. Lixisenatide
    D. Liraglutide

26. A 58-year-old woman with a medical history significant for osteoporosis and T2DM (6 years) receives metformin

1000 mg twice daily for DM management. Her A1C today is 7.9%, fasting BG is 80–98 mg/dL, and 2-hour postprandial BG is 194–210 mg/dL. Adding which one of the following would best assist this patient in achieving her glycemic goals?

A. Saxagliptin 5 mg once daily
B. Canagliflozin 100 mg daily
C. Insulin detemir 10 units once daily
D. Pioglitazone 15 mg daily

27. A 35-year-old woman (BMI 30 kg/m^2) was given a diagnosis of T2DM 5 years ago. She receives therapy with metformin 1000 mg twice daily (5 years), canagliflozin 100 mg daily (3 months), and sitagliptin 100 mg daily (6 weeks). Today in the clinic, her A1C is 6.1%; average fasting/postprandial is BG 80–100 mg/dL. The patient has new-onset joint pains of the knees, which she describes as progressively severe. She has been unable to walk more than 5 feet without extreme discomfort over the past 2 weeks and needed a walker to come to the clinic. Acetaminophen did not provide any relief. Which one of the following is best to recommend this patient discontinue?

A. Canagliflozin
B. Sitagliptin
C. Metformin
D. Canagliflozin and sitagliptin

28. A patient taking exenatide extended release 2 mg subcutaneously every Monday at 9 a.m. calls the pharmacy on Wednesday at 9 a.m. because he missed his weekly dose. Which one of the following is best to recommend for this patient?

A. Administer the missed dose now; continue with your regimen Monday.
B. Omit the dose this week; administer the next dose Monday.
C. Administer the missed dose now; omit the next dose Monday.
D. Omit the dose this week; administer twice the dose Monday.

29. A 68-year-old woman with T2DM (weight 68 kg [150 lb]) has and A1C of 7.3%, an average BG of 100 mg/dL, CrCl (Cockcroft-Gault) 50 mL/minute, and stable SCr (1.6 mg/dL). She has a history of hypertension controlled on lisinopril 20 mg daily for 10 years and T2DM controlled on metformin 500 mg twice daily (x 10 years) and canagliflozin 300 mg daily (x 1 month). She describes new-onset dizziness, weakness, and lightheadedness for the past 3 weeks but denies symptoms of hypoglycemia. The patient denies recent weight loss. Her home blood pressure measurements have been 90–94/58–60 mm Hg over the past 3 weeks. Which one of the following is best to recommend for this patient?

A. Reduce the canagliflozin dose.
B. Discontinue lisinopril.
C. Reduce the lisinopril dose and discontinue canagliflozin.
D. Reduce the canagliflozin dose and discontinue lisinopril.

30. A 78-year-old woman (weight 64 kg [140 lb]) with a medical history significant for T2DM and hypertension (6 years) presents for a follow-up visit. Her A1C is 7%, eGFR is 50 mL/minute/1.73 m^2, and average blood pressure is 120/78 mm Hg. The patient currently takes metformin 1000 mg twice daily (6 years), canagliflozin 300 mg (3 months), lisinopril 10 mg daily (6 years), triamterene/hydrochlorothiazide 37.5/25 mg daily (6 years), and amlodipine 5 mg daily (6 years). She states that she is tolerating all of her drugs well. Her most recent pertinent chemistry results were SCr 1.6 mg/dL, BG 130 mg/dL, and K 5.0 mEq/L. Which one of the following is best to recommend for this patient?

A. Discontinue metformin and canagliflozin
B. Decrease canagliflozin to 100 mg once daily and metformin to 500 mg daily
C. Discontinue lisinopril and triamterene/hydrochlorothiazide
D. Decrease canagliflozin to 100 mg once daily and monitor potassium concentrations

31. A 49-year-old man (weight 135 kg [298 lb]) with T2DM (A1C 1 week ago was 9.2%) has a medical history significant for hypertension, dyslipidemia, heart failure with reduced ejection fraction (HFrEF) (EF 40%), pancreatitis, and peptic/colonic ulceration x 2. He currently takes metformin 1000 mg twice daily. Which one of the following is best to recommend initiating for this patient?

A. Lixisenatide
B. Linagliptin
C. Pioglitazone
D. Insulin glargine U-100

32. A 61-year-old man has a medical history significant for T2DM (complicated by neuropathy and nephropathy) and hypertension. His A1C today is 10%. The patient's current DM regimen is metformin 500 mg twice daily. He admits symptoms of hyperglycemia for the past month but denies symptoms of hypoglycemia. He checks his BG once a day, but he did not bring in his glucometer or logbook to today's clinic visit. The patient has lost 11 kg (25 lb) over the past 3 months by changing his diet and increasing his physical activity. He tells you he is motivated to continue losing weight. His other laboratory values from today are as follows: eGFR 40 mL/minute/1.73 m^2, Na 138 mEq/L, K 5.1 mmol/L, LDL 86 mg/dL, TG 150 mg/dL, HDL 42 mg/dL, TC 158 mg/dL, and microalbumin

240 mcg/mg. Which one of the following is best to recommend initiating for this patient?

A. Dapagliflozin
B. Insulin glargine U-100
C. Sitagliptin
D. Insulin lispro U-100 with meals

33. A 48-year-old woman (weight 54 kg [120 lb]) has T2DM (current A1C 7.9%), HFrEF (EF 25%), hypertension, and frequent UTIs. She takes metformin 1000 mg twice daily and glipizide 10 mg twice daily for her DM management, and she does not want to use an injection for management. Which one of the following is best to recommend adding to this patient's regimen?

A. Sitagliptin
B. Empagliflozin
C. Pioglitazone
D. Exenatide

34. A 55-year-old woman (weight 125 kg [276 lb]) with newly diagnosed T2DM (A1C 8%) is initiated on metformin therapy. She presents today with complaints of severe diarrhea and abdominal pain, which did not resolve after 3 weeks of therapy. She has stopped taking metformin and is unwilling to restart it. Her medical history is significant for obesity, hypertension, and a history of recurrent yeast infections. Which one of the following is best to recommend initiating for this patient?

A. Glipizide
B. Empagliflozin
C. Liraglutide
D. Pioglitazone

35. A 72-year-old man (weight 100 kg [220 lb]) with T2DM currently takes metformin 1000 mg twice daily and sitagliptin 100 mg daily. He has been adherent to this regimen for 5 years, and his most recent A1C 1 month ago was 6.9%. He is now given a diagnosis of HFrEF (EF 35%). Which one of the following is best to recommend for this patient?

A. Discontinue sitagliptin.
B. Discontinue sitagliptin and initiate alogliptin.
C. Discontinue sitagliptin and initiate saxagliptin.
D. Continue current regimen.

36. A 51-year-old woman (weight 160 kg [352 lb]) with T2DM has a prescribed regimen of metformin 1000 mg twice daily and insulin glargine U-100 - 76 units in the evening. She admits missing her insulin dose on average twice a week because of her busy schedule. She checks her BG three times a day. When she remembers to take her insulin, her BG values are as follows: fasting plasma glucose 120–130 mg/dL, pre-dinner BG 130–145 mg/dL, and 2-hour postprandial BG (dinner) 200–220 mg/dL. On the days she forgets to take insulin, her BG values are in the 200s. Which one of the following is best to recommend for this patient?

A. Change to insulin glargine U-300 in the evening.
B. Initiate insulin lispro U-200 at dinner.
C. Change to premixed insulin degludec/insulin aspart at dinner.
D. Initiate Technosphere insulin at dinner.

37. An 82-year-old man (weight 91 kg [200 lb]) has a medical history significant for T2DM (A1C 3 months ago was 8.3%), stage 4 CKD (eGFR 24.1 mL/minute/1.73 m^2), HFrEF (EF 35%), hypertension, and dyslipidemia. His current DM regimen is insulin glargine U-100 - 56 units at bedtime; he has taken this for 1 year with no changes. Today, he has complaints of excessive sweating and heart palpitations occurring overnight around 2 a.m.; these have caused him to wake up for the past 2 weeks. He tells you his symptoms usually resolve with a snack. He currently checks his BG values twice a day and reports 100% adherence to his drug regimen. His 14-day average fasting plasma glucose is 200 mg/dL, and his 14-day average pre-dinner BG value is 120 mg/dL. Which one of the following is best to recommend for this patient?

A. Initiate metformin.
B. Change to insulin degludec U-100.
C. Initiate saxagliptin.
D. Change to insulin glargine U-300.

38. A 49-year-old man (weight 132 kg [290 lb]) presents for a follow-up appointment. His medical history is significant for T2DM, hypertension, and dyslipidemia. His current DM regimen is metformin 1000 mg twice daily and insulin glargine U-100 - 60 units at bedtime. Today, he complains of polyuria (8–10 times/day) and polydipsia over the past 4 months. He checks his BG values once a day first thing in the morning and brought in his logbook today for your review (average fasting plasma glucose over the past 3 months is 208 mg/dL); he is unwilling to check his BG more than once a day. His last A1C (2 weeks ago) was 8.9%. Which one of the following is best to recommend adding to this patient's regimen?

A. Glipizide
B. Insulin aspart
C. Sitagliptin
D. Liraglutide

39. A 48-year-old woman (weight 100 kg [220 lb]) presents for an initial appointment to establish care. Records from her previous provider show that her medical history is significant for T2DM (A1C 3 days ago was 9.5%), resistant hypertension, dyslipidemia, and lymphedema. Her current DM regimen is metformin 1000 mg twice daily and insulin glargine 70 units at bedtime. She denies any complaints with her insulin injection and reports 100%

medication adherence. Today, she admits symptoms of hyperglycemia but denies hypoglycemia. She consumes from one to three meals inconsistently per day, depending on her work schedule. She currently checks her BG three times a day and brought in her logbook for you to review; her self-monitoring BG (averages over the past 7 days) are fasting plasma glucose 180 mg/dL, pre-lunch 220 mg/dL, and bedtime 280 mg/dL. Which one of the following is best to recommend for this patient?

A. Increase insulin glargine U-100.
B. Discontinue insulin glargine and initiate insulin degludec/insulin aspart.
C. Initiate insulin aspart at breakfast and dinner.
D. Change to insulin glargine U-300.

40. A 41-year-old woman (weight 73 kg [160 lb]) with T2DM currently takes insulin glargine U-100 - 70 units twice daily and insulin lispro 26 units with meals. She does not take metformin because of tolerability issues. Although she is adherent to her regimen, she is frustrated with the number of injections she takes per day. She is inconsistent with her meals and appropriately skips her mealtime insulin when she does not eat. She checks her BG four times a day. Her 30-day BG averages as are follows: fasting plasma glucose 200 mg/dL, pre-lunch 220 mg/dL, pre-dinner 190 mg/dL, and 2-hour postprandial glucose (dinner) 260 mg/dL. Which one of the following is best to recommend for this patient?

A. Change basal insulin to insulin degludec U-200 and increase dose and continue insulin lispro.
B. Change basal and bolus insulin to premixed insulin degludec/insulin aspart and increase dose.
C. Increase the insulin glargine U-100 dose.
D. Initiate dulaglutide.

LEARNER CHAPTER EVALUATION: NEW PHARMACOTHERAPIES FOR TYPE 2 DIABETES.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

20. The content of the chapter met my educational needs.
21. The content of the chapter satisfied my expectations.
22. The author presented the chapter content effectively.
23. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
24. The content of the chapter was objective and balanced.
25. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
26. The content of the chapter was useful to me.
27. The teaching and learning methods used in the chapter were effective.
28. The active learning methods used in the chapter were effective.
29. The learning assessment activities used in the chapter were effective.
30. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

31. Distinguish between the medication therapy recommendations in the updated 2016 diabetes clinical guidelines.
32. Evaluate the role of incretin-based therapies such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase-4 (DPP-4) inhibitors and the sodium-glucose cotransporter-2 (SGLT-2) inhibitors for the treatment of type 2 diabetes.
33. Discuss the cardiovascular safety and efficacy of the DPP-4 inhibitors, GLP-1 RAs, and SGLT-2 inhibitors.
34. Delineate the role and place in therapy of new insulin therapies in the treatment of type 2 diabetes.
35. Please provide any specific comments relating to any perceptions of bias, promotion, or advertisement of commercial products.
36. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Questions 37–39 apply to the entire Endocrinology I learning module.

37. How long did it take you to read the instructional materials in this module?
38. How long did it take you to read and answer the assessment questions in this module?
39. Please provide any additional comments you may have regarding this module:

Endocrinology II

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Adrenal Insufficiency, Cushing Syndrome, and Hyperaldosteronism

By Dana A. Brown, Pharm.D., BCPS; and Amy M. Henneman, Pharm.D., BCPS, CDE

Reviewed by Eric A. Dietrich, Pharm.D., BCPS; and Jodi Peoples, Pharm.D., BCPS

LEARNING OBJECTIVES

1. Using knowledge of the etiology and pathophysiology of adrenal disorders, classify the type of disorder (e.g., adrenal insufficiency, Cushing syndrome, hyperaldosteronism) for a given patient.
2. Recommend diagnostic testing for a patient with an adrenal disorder.
3. Develop and/or modify a treatment plan including pharmacologic and nonpharmacologic therapies for a patient with an adrenal disorder.
4. Evaluate adverse effects and monitoring values associated with treatments for adrenal disorders.
5. Devise a counseling plan considering both short- and long-term effects of treatment for a given patient with an adrenal disorder.

ABBREVIATIONS IN THIS CHAPTER

AA	Aldosterone antagonist
ACTH	Adrenocorticotropic hormone
ARR	Aldosterone-to-renin ratio
CRH	Corticotropin-releasing hormone
DST	Dexamethasone suppression test
FST	Fludrocortisone suppression testing
HPA	Hypothalamus-pituitary-adrenal (axis)
PAC	Plasma-aldosterone concentration
PAI	Primary adrenal insufficiency
PRA	Plasma-renin activity
SAI	Secondary adrenal insufficiency
TSS	Transsphenoidal selective adenomectomy
UFC	Urinary free cortisol

Table of other common abbreviations.

INTRODUCTION

The term *adrenal disorders* collectively refers to any conditions stemming from a problem related to the adrenal gland or its functioning. Because the pituitary gland secretes hormones that directly control the adrenal gland, the over- or under-secretion of hormones by the pituitary gland, benign or malignant tumors in the pituitary and/or adrenal glands, or genetic mutations may lead to the development of an adrenal disorder. This chapter focuses on recognizing and managing adrenal insufficiency, Cushing syndrome, and hyperaldosteronism.

HORMONE PRODUCTION AND REGULATION

Anatomy of the Adrenal Gland

Each adrenal gland, situated on the upper poles of the kidneys, is surrounded by a fibrous capsule and composed of two endocrine glands: the medulla and the cortex (Figure 1-1). The medulla consists mainly of chromaffin cells, which are part of the sympathetic nervous system and account for 10% of the adrenal gland. Specifically, the medulla is the location for the conversion of tyrosine to epinephrine, norepinephrine, and dopamine. The adrenal cortex, composing the remaining 90% of the adrenal gland, is responsible for hormone secretion. Three concentric zones exist within the adrenal cortex: zona glomerulosa, zona fasciculata, and zona reticularis. The zona glomerulosa accounts for 15% of the adrenal cortex and is responsible for producing aldosterone, which maintains the homeostatic balance of electrolytes, including the renal tubular reabsorption of sodium. The zona fasciculata accounts for 60% of the adrenal cortex

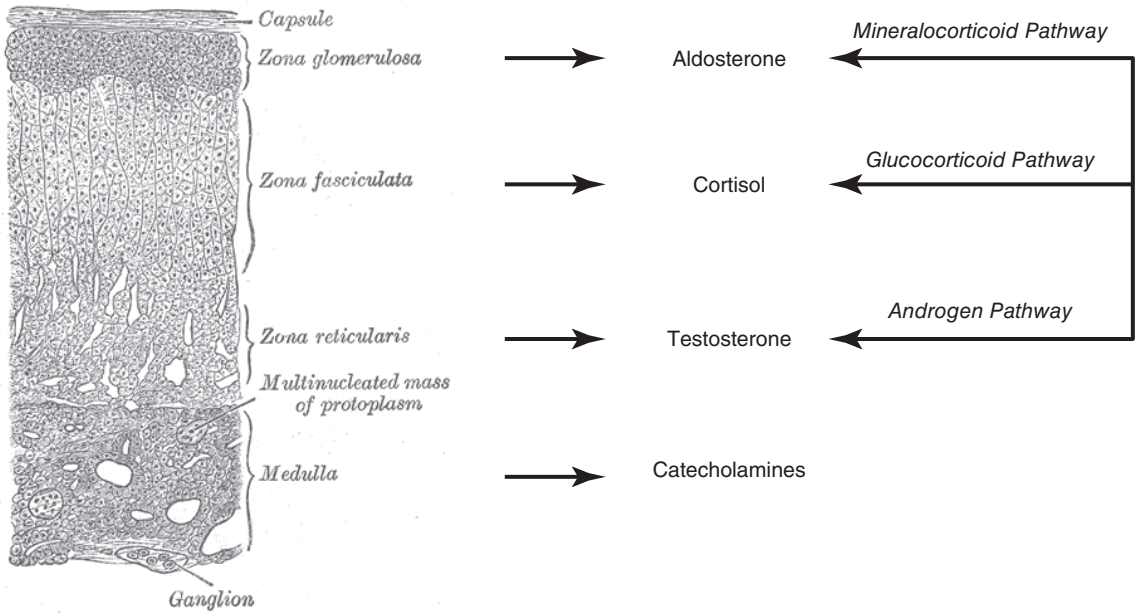

Figure 1-1. Zones of the adrenal gland and their hormones.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the physiology of the adrenal gland and axis
- Differences in the types of adrenal disorders
- Knowledge of the drugs used to treat adrenal disorders
- The association between corticosteroid usage and adrenal axis suppression

Table of common laboratory reference values

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Funder JW, Carey RM, Mantero F, et al. The management of primary aldosteronism: case detection, diagnosis and treatment: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2016;101:1889-916.
- Nieman LK, Biller BMK, Findling JW, et al. The diagnosis of Cushing's syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2008;93:1526-40.

and is responsible for cortisol secretion. The innermost zone is the zona reticularis, which accounts for the remaining 25% of the adrenal cortex and produces androgens.

Regulation of Hormone Production and Secretion

Under normal conditions, homeostasis of steroid secretion is regulated through the hypothalamus-pituitary-adrenal (HPA) axis (Figure 1-2). When plasma concentrations of these hormones are insufficient to meet the body's needs, the hypothalamus releases corticotropin-releasing hormone (CRH), which stimulates the anterior pituitary gland to release adrenocorticotropic hormone (ACTH). This hormone acts directly on the adrenal gland to produce largely cortisol and, to a lesser degree, androgens and aldosterone. Secretion of ACTH may be triggered by pain, surgery, hypothermia, hypoxia, or stress. Elevated concentrations of cortisol and/or androgens exert a negative feedback on the secretion of CRH and ACTH, ceasing their production.

Aldosterone production and secretion is quite complex because it is mediated not only by the HPA axis but also by the renin-angiotensin-aldosterone system. Production of angiotensin II from renin is the main impetus for aldosterone production. Renin production is regulated by factors such as changes in volume, blood pressure, sodium concentrations, posture, and drugs, among others. Angiotensin II may further be converted to angiotensin III by an aminopeptidase. Both

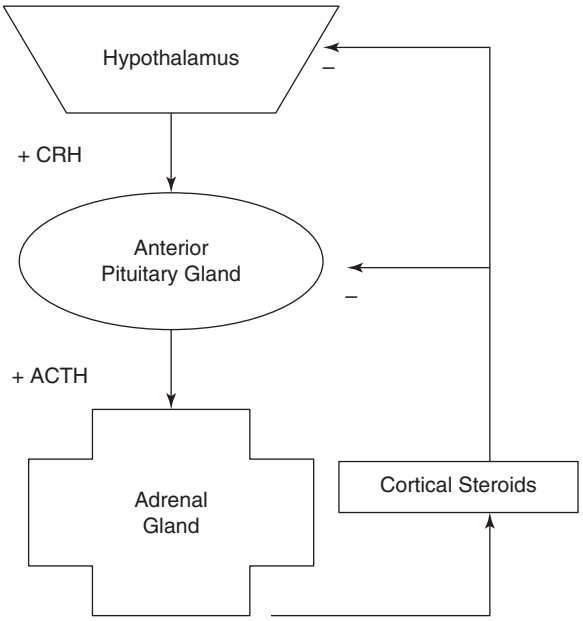

Figure 1-2. Hypothalamus-pituitary-adrenal axis and negative feedback.

ACTH = adrenocorticotropic hormone; CRH = corticotropin-releasing hormone.

angiotensin II and angiotensin III stimulate the zona glomerulosa to release aldosterone. Once secreted, aldosterone causes the kidneys to increase sodium and water retention as well as increase blood pressure, exerting a negative feedback on renin's release.

HYPOFUNCTION OF THE ADRENAL GLAND

Primary Adrenal Insufficiency

Epidemiology/Etiology

Primary adrenal insufficiency (PAI), or Addison disease, is a severe and potentially life-threatening condition in which the adrenal cortex does not produce a sufficient amount of glucocorticoids, mineralocorticoids, and dehydroepiandrosterone. Primary adrenal insufficiency is rare, with estimates of 4.4–6 new cases per 1 million people per year. It occurs more commonly in women than in men for reasons unknown. Addison disease may occur at any age, but most patients receive diagnoses at age 30–50 years. There are many potential causes or precipitating factors leading to PAI, and in developed countries, 80%–90% of cases can be attributed to autoimmune adrenalitis. Of those in which autoimmune disease is found, 60% will have autoimmune polyendocrinopathy syndrome in which other autoimmune diseases are likely to be present (Charmandari 2014; Arlt 2009). Other, less common etiologies of PAI include tuberculosis adrenalitis, which is still a major cause in developing countries today; adrenal hemorrhage, which is most often associated with antiphospholipid syndrome or trauma; and genetic disorders (Arlt 2003). In addition, drugs that inhibit the synthesis of cortisol, such as ketoconazole, or drugs that increase the metabolism of cortisol, such as phenytoin or rifampin, may lead to the development of PAI. The estimated life expectancy of patients with PAI is reduced by 3.2 years for women and 11.2 years for men versus the general population, even with appropriate treatment (Johannsson 2015).

Symptoms/Clinical Presentation

Symptoms of PAI may be acute in onset or may begin months to years before diagnosis. Symptoms of a chronic onset are often insidious; therefore, many may not be recognized until the patient presents in an adrenal crisis. The most common symptoms of PAI include weight loss, hypotension, hypovolemia, dizziness, fatigue, reduced muscle strength, and abdominal pain with or without nausea and vomiting. Patients will also have patchy hyperpigmentation of the skin that is often subject to pressure or stress. Areas include the elbows, knuckles, creases of the palms of the hands and feet, lips, and buccal mucosa. Serum chemistries may indicate mild hyponatremia accompanied by mild hyperkalemia and increased SCr, and in 10%–20% of patients, mild hypercalcemia has been reported (Husebye 2014). Anemia, eosinophilia, and lymphocytosis may also be present. In patients presenting in adrenal crisis, these symptoms are more severe and often accompanied by confusion, loss of consciousness, and coma. Because dehydroepiandrosterone is also decreased in patients with PAI, patients may present with loss of axillary and pubic hair as well as decreased libido, particularly women, because the adrenal glands are the main source of dehydroepiandrosterone production (Arlt 2003).

Diagnosis

Because the symptoms associated with PAI are insidious, many patients may go without a diagnosis. In patients who present with signs and symptoms consistent with adrenal crisis, treatment should be initiated as soon as possible, before results of diagnostic testing. Blood samples should be collected before initiating treatment so that baseline serum cortisol and ACTH values can be obtained, if possible. The diagnostic test of choice in patients with suspected PAI is the standard-dose, 250-mcg corticotropin stimulation test (Bornstein 2016). After 30 or 60 minutes, the patient's peak cortisol concentration should be greater than 18 mcg/dL. Anything less than this indicates adrenal insufficiency. Exogenous corticosteroid use, either oral or inhaled, will affect serum cortisol values and may impair interpretation of results. A baseline plasma ACTH, renin, and aldosterone should also be collected to determine whether the adrenal insufficiency is primary or secondary and to aid in establishing a specific etiology. Patients with PAI are expected to have an ACTH value greater than 2 times the upper limit of the reference range

(9–52 pg/mL). In addition, mineralocorticoid deficiency is expected in a patient with PAI, as evidenced by low serum aldosterone and plasma-renin activity (PRA), which should be obtained together with baseline ACTH (Bornstein 2016). The low-dose corticotropin stimulation test, 1 mcg, should be reserved for use only when the standard dose is not available because it lacks the validity of the standard-dose corticotropin stimulation test (Bornstein 2016; Charmandari 2014). To distinguish the etiology of the PAI further, a CT scan of the adrenal glands may be done to rule out adrenal hemorrhage, tumor, or tuberculosis adrenalitis. Detection of antibodies, such as 21-hydroxylase autoantibodies or CYP21A2 autoantibodies, as well as identification and diagnosis of other concomitant autoimmune diseases that may be present will assist in establishing an etiology of autoimmune origins. Assays for detecting autoantibodies for adrenal insufficiency are not standardized; therefore, variation between assays is common (Bornstein 2016; Husebye 2014). Figure 1-3 is a diagnostic algorithm of suspected adrenal insufficiency. A quick reference guide on diagnosing Addison disease is available online.

Secondary Adrenal Insufficiency

Epidemiology/Etiology

Secondary adrenal insufficiency (SAI) has been estimated to occur at a prevalence of 150–280 cases per 1 million people (Arlt 2003). However, because exogenous administration of corticosteroids is one of the main precipitating factors for SAI, the prevalence may be underestimated. Patients with

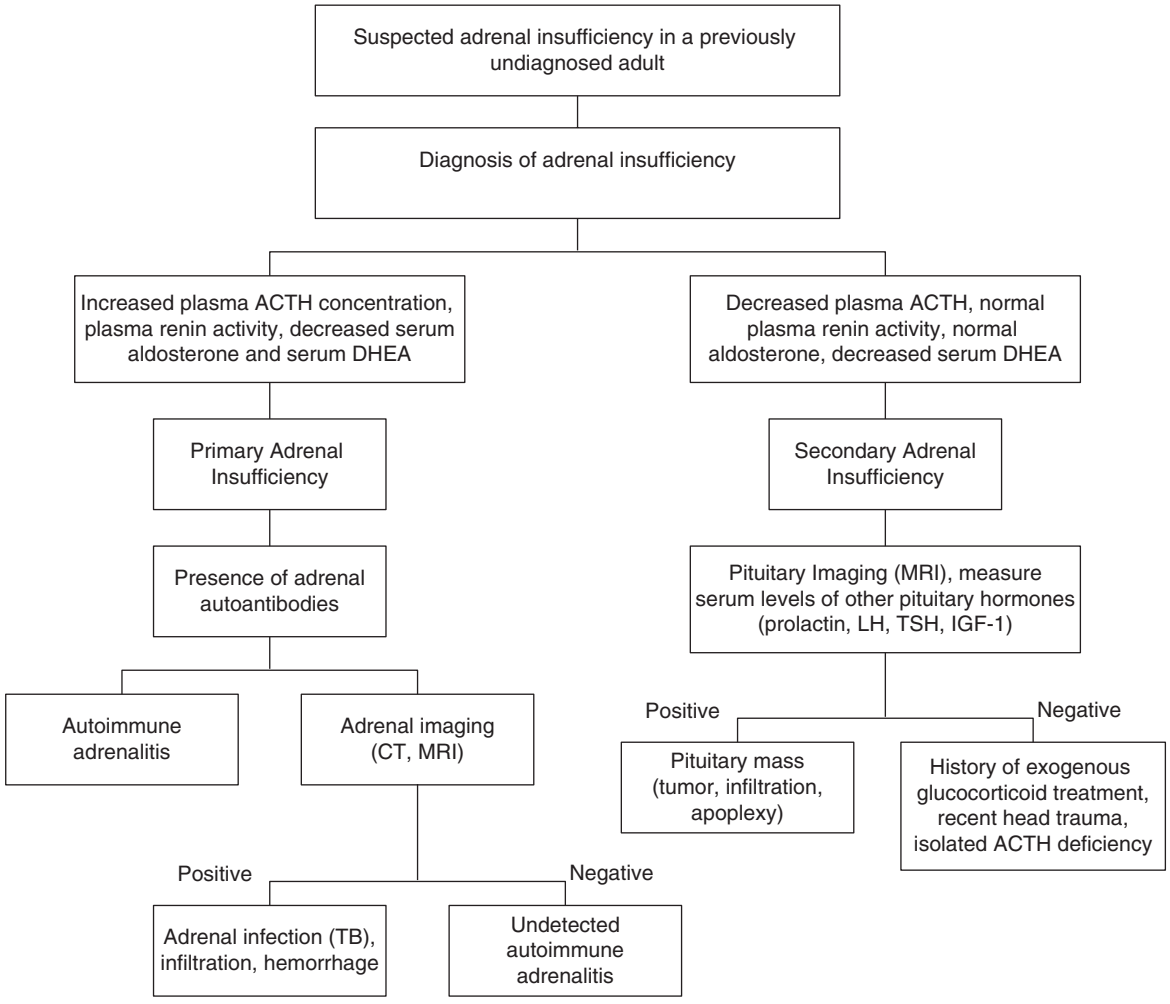

Figure 1-3. Diagnostic algorithm for adrenal insufficiency.

DHEA = dehydroepiandrosterone; IGF-1 = insulin-like growth factor 1; LH = luteinizing hormone; TB = tuberculosis; TSH = thyroid-stimulating hormone.

Information from: Arlt W. The approach to the adult with newly diagnosed adrenal insufficiency. J Clin Endocrinol Metab 2009;94:1059-67.

SAI will have not only decreased serum cortisol but also decreased ACTH. Other secondary causes of adrenal insufficiency include tumors within the hypothalamus or pituitary glands, pituitary irradiation, and autoimmune origins (Arlt 2003). Pituitary adenomas are most common; however, craniopharyngiomas, meningioma, or granulomatous disease and pituitary apoplexy may occur rarely (Arlt 2009). Glucocorticoid-induced HPA axis suppression has been reported with many dosage forms and treatment durations (Joseph 2016; Dinsen 2013). Patients receiving more than 7.5 mg of prednisone dose equivalents daily for more than 3 weeks are at greater risk (Duru 2013). The HPA axis suppression associated with corticosteroid use may be short-lived, but it may also last a year or more (Dinsen 2013).

Symptoms/Clinical Presentation

Patients with SAI will present similarly to patients with PAI. Signs and symptoms include fatigue, weight loss, reduced muscle strength, and abdominal pain with or without nausea and vomiting. In addition, patients with SAI often have very pale skin, and the hyperpigmentation seen in PAI does not occur (Arlt 2003). Because mineralocorticoid secretion is preserved in these patients, the volume depletion and electrolyte abnormalities common in PAI are not expected in patients with SAI. In patients with SAI because of tumor or other direct insult to the pituitary gland, other pituitary hormones may be decreased, leading to more severe symptoms such as hypovolemia, cold intolerance, increased thirst, and frequent urination. Patients with pituitary apoplexy, a sudden neurological impairment because of pituitary dysfunction, and a pituitary tumor may present with headache. Those with pituitary apoplexy will present with a severe headache of sudden onset (Arlt 2009).

Diagnostics

In patients with prior pituitary disease, diagnosis of SAI will occur according to the history of pituitary disease and accompanying signs and symptoms. In patients without prior pituitary disease, a careful history should be taken to rule out the possibility of glucocorticoid-induced HPA axis suppression. The standard-dose, 250-mcg corticotropin stimulation test alone cannot confirm SAI. In patients with SAI caused by central HPA axis suppression, recent-onset adrenal insufficiency may not be detected with this test. Depending on the length of dysfunction, the adrenal glands may not have atrophied and may still respond in a normal or near-normal manner to stimulation (Krasner 1999). The CRH stimulation test or the insulin-induced hypoglycemia test should be used as a follow-up in patients with suspected SAI. The CRH stimulation test involves administering CRH at a dose of 1 mcg/kg, followed by measuring serum cortisol and corticotropin every 15–30 minutes for up to 2 hours. Patients with SAI will have little to no corticotropin response (Charmandari 2014). The insulin hypoglycemia test requires regular insulin administered at a dose of 0.1–0.15 units/kg, inducing a symptomatic hypoglycemic state, typically a blood glucose less than 60 mg/dL. Serum glucose and cortisol are measured every 15–30 minutes for 90–120 minutes. A peak cortisol less than 500 nmol/L is diagnostic of adrenal insufficiency (Charmandari 2014; Arlt 2003). Although the insulin-induced hypoglycemia test has been considered the diagnostic test of choice in the past, risks associated with hypoglycemic induction, particularly in older adults or those with a history of cardiovascular disease or seizure disorders, have led to preference of the CRH stimulation test by many. The results of both the CRH stimulation test and the insulin hypoglycemia test correlate well with the diagnosis of SAI (Schlaghecke 1992). The overnight metyrapone test may also be used to establish a diagnosis of SAI. This test requires metyrapone administration at a dose of 30 mg/kg at midnight. Eight hours after metyrapone administration, an 11-deoxycortisol assay should be measured. In patients with SAI, 11-deoxycortisol will not exceed 200 nmol/L (Arlt 2003). Both the insulin hypoglycemia test and the metyrapone diagnostic test require close inpatient monitoring. A standard assay for 11-deoxycortisol, measured in the metyrapone stimulation test, has not been established.

Serum dehydroepiandrosterone will be low in SAI as well as in PAI (Lang 2015). Because mineralocorticoid secretion is not affected in SAI, serum aldosterone concentrations and PRA should be normal in these patients. If SAI occurs because of unknown origin, MRI is the method of choice to identify the presence of a tumor within the hypothalamic-pituitary region or the presence of pituitary apoplexy (Arlt 2003). Serum prolactin, thyroid-stimulating hormone, insulin-like growth factor 1, and luteinizing hormone may also be measured to identify pituitary dysfunction (see Figure 1-3) (Arlt 2009).

Adrenal Crisis

Adrenal crisis is life threatening and requires immediate medical attention. The initial presentation may be nonspecific and usually occurs in patients with underlying undiagnosed or inadequately treated adrenal insufficiency. It may be the patient's initial presentation leading to a diagnosis of either PAI or SAI. Adrenal crisis has an incidence rate of 6.3 crises per 100 patient-years in patients with either PAI or SAI (Hahner 2010). About 1 in 12 patients with adrenal insufficiency will have an adrenal crisis each year (Bornstein 2016).

Precipitating Factors

In patients with previously diagnosed adrenal insufficiency, adrenal crisis usually occurs because of a lack of corticosteroid dosage adjustment by patients or practitioners during increased physiologic stress (Arlt 2003). These episodes are usually precipitated by surgery, critical illness, extreme emotional distress, climatic changes with prolonged exposure to heat, trauma, or pregnancy. Gastrointestinal infection and fever are the most commonly cited illnesses associated with precipitating an adrenal crisis (Hahner 2010). Initiating a

medication that alters the clearance of cortisol may also precipitate adrenal crisis in some patients (Bornstein 2016).

Clinical Presentation

Patients usually present with marked hypotension, or shock, which, in patients with PAI, is accompanied by significant volume depletion. Other signs and symptoms include severe weakness, abdominal pain that may be accompanied by nausea and vomiting, and fever. Patients presenting with adrenal crisis often have a blunted response to catecholamines until glucocorticoid replacement has been initiated (Arlt 2003).

Treatment

Corticosteroids

The mainstay of treatment for adrenal insufficiency is corticosteroid replacement. Under normal physiological circumstances, cortisol begins to rise at 2:00–4:00 a.m. each day. It typically peaks 1 hour after waking and then begins a gradual decline that persists the rest of the day. Cortisol concentrations reach their lowest values around midnight. Daily cortisol secretion is 5–10 mg/m^2 (Esteban 1991). Clinicians and patients are challenged to administer an exogenous corticosteroid in a manner that mimics natural cortisol secretion as closely as possible while avoiding over- or under-replacement. In addition, during increased stress, the body naturally increases its production of cortisol in response to the added stressor. Knowing when and by how much to increase corticosteroid dosing during these times has proven challenging.

Hydrocortisone or cortisone acetate is the preferred glucocorticoid for replacement in patients with PAI or SAI because of their shorter half-lives and lower glucocorticoid potency, thus potentially minimizing the incidence of unwanted adverse metabolic effects. Both also exert higher mineralocorticoid effects than other available corticosteroids, decreasing the fludrocortisone dose requirement in patients with PAI (Bornstein 2016; Arlt 2009). The pharmacokinetic variability of cortisone acetate is greater than that of hydrocortisone because it needs to be activated by the liver. Hydrocortisone should be given in two or three divided doses at a total daily dose of 15–25 mg daily. The largest dose, one-half to two-thirds, should be given in the morning, the second early afternoon, and, if a third dose is used, the late afternoon (Bornstein 2016; Charmandari 2014). The last dose should be given a minimum of 4–6 hours before bedtime to avoid interfering with the patient's sleep as well as to minimize adverse effects on glucose homeostasis. Hydrocortisone is a CYP3A4 substrate; therefore, patients initiated on CYP3A4 inducers should expect to increase their hydrocortisone dosage, and those initiated on CYP3A4 inhibitors may need to decrease their corticosteroid dosage.

Prednisolone and dexamethasone are not recommended first line because of their longer half-lives and increased glucocorticoid potency, which may result in signs and symptoms of glucocorticoid excess, effects on insulin sensitivity and bone mineral density, and higher nighttime glucocorticoid activity, which may result in insomnia (Arlt 2009). However, data regarding these effects are lacking, with only a few small studies noting potential differences in metabolic outcomes and bone mineral density with either prednisolone or dexamethasone (Schulz 2016; Filipsson 2006; Jodar 2003). Prednisolone and dexamethasone exert little to no activity on mineralocorticoid receptors, which may result in higher mineralocorticoid replacement dosages needed in patients with PAI (Arlt 2009). Prednisolone may be an appropriate alternative in patients who have difficulty adhering to multidose regimens, patients who continue to have poor quality of life despite adequate corticosteroid replacement, or those with coexisting insulin-dependent diabetes (Bornstein 2016; Arlt 2009).

Dose adjustments should be made on the basis of patient assessment. Signs of over-replacement include weight gain, insomnia, and peripheral edema. Signs of under-replacement include poor appetite, nausea, weight loss, lethargy, and hyperpigmentation of the skin (Bornstein 2016; Oksnes 2015). During increased stress or intercurrent illness, corticosteroid dosages should be increased. For febrile illness, the daily dose may be doubled or tripled until recovery. For surgery, increased dosages of 50–100 mg/day have been suggested (Hahner 2009; Salem 1994).

Patients with SAI as the result of glucocorticoid-induced HPA axis suppression may recover over time. These patients should be treated like others with diagnosed adrenal insufficiency, receiving daily physiologic corticosteroid replacement doses as well as increased dosing during extreme stress (Duru 2013; Krasner 1999).

Choice of corticosteroid affects the degree of HPA axis suppression. Hydrocortisone and cortisone acetate are considered the least suppressive, whereas prednisone, prednisolone, methylprednisolone, triamcinolone, and dexamethasone have greater suppressive effects on the HPA axis. Dexamethasone is considered to have the longest duration of HPA axis suppression because of its long half-life (Krasner 1999). No controlled clinical trials exist to recommend one method of tapering over another. Changing a patient to hydrocortisone and then beginning a tapering regimen has been suggested as a way to minimize the risk of glucocorticoid-induced HPA axis suppression. Patients beginning corticosteroid tapering and withdrawal should be instructed to contact their physician immediately, should they start to feel unwell or have any signs or symptoms of adrenal insufficiency.

In patients with adrenal crisis, glucocorticoid replacement should be initiated immediately through an intravenous infusion. A bolus dose of 100 mg of intravenous hydrocortisone should be given initially, followed by hydrocortisone 100–200 mg daily by either continuous infusion or divided doses every 6 hours in addition to supportive care (Bornstein 2016; Arlt 2003). If hydrocortisone is unavailable, guidelines recommend prednisolone as an appropriate alternative for patients with PAI (Bornstein 2016). Once the patient is

stabilized and conscious, treatment with an oral corticosteroid at the recommended dosage range of 15–25 mg daily hydrocortisone should be resumed before discharge.

Adverse effects of corticosteroids include edema, GI upset, menstrual irregularities, impaired glucose tolerance, hypertension, dyslipidemia, increased intraocular pressure, and increased susceptibility to infections, acne, impaired wound healing, muscle weakness and atrophy, and osteoporosis. Adverse effects from exogenous administration of corticosteroids can be many. In adrenal insufficiency, overall replacement dosages are low, minimizing the occurrence of adverse effects. Many of these adverse effects occur because of supraphysiological dosages of corticosteroids. Patients with these adverse effects should be assessed for adequate corticosteroid replacement that mitigates signs of under-replacement and minimizes many of these adverse effects, which can be signs of over-replacement. Dose reductions should be made, if necessary.

Daily vs. Alternate-Day Dosing

Patients undergoing treatment for diagnosed adrenal insufficiency, either primary or secondary, should be prescribed corticosteroid replacement to be taken on a daily basis. Alternate-day dosing has been suggested as a means of decreasing the risk of HPA axis suppression in patients prescribed long-term or high-dose corticosteroids. However, the risk of HPA axis suppression is not prevented using alternate-day corticosteroid dosing (Duru 2013).

Mineralocorticoids

Patients with PAI will require mineralocorticoid replacement with fludrocortisone in addition to glucocorticoid replacement. Fludrocortisone starting at 50–100 mcg is recommended. Patients taking either prednisolone or dexamethasone will require higher overall fludrocortisone dosages because these glucocorticoids have little to no mineralocorticoid activity compared with hydrocortisone (Quinkler 2015). The dose should be taken once daily in the morning because mineralocorticoids follow a circadian pattern similar to that of glucocorticoids. In addition, patients should be counseled not to restrict their sodium intake. When patients are in a hot climate or under conditions promoting excessive sweating, temporary dose increases of 50%–100% of the patient's usual dose should be recommended (Quinkler 2015; Hahner 2009). During adrenal crisis, mineralocorticoid administration is not necessary as long as the patient is receiving more than 50 mg of hydrocortisone daily because of hydrocortisone's inherent mineralocorticoid activity. Fludrocortisone should be resumed once the hydrocortisone dose is less than 50 mg/day (Bornstein 2016; Quinkler 2015).

In a patient with PAI who develops hypertension, both the glucocorticoid and mineralocorticoid dosages should be assessed. If no other symptoms are noted, the fludrocortisone dosage should be decreased. However, the patient's salt cravings and blood pressure should be monitored carefully. In patients whose blood pressure remains elevated despite a decrease in the fludrocortisone dose and appropriate glucocorticoid dosing, an antihypertensive medication should be added (Bornstein 2016).

Adverse effects associated with fludrocortisone use include hypertension, edema, and hypernatremia or hyperkalemia. When the patient receives an appropriate replacement dose, these effects should be minimal.

Supportive Care

In women, the adrenal glands are a major source of androgen production. Therefore, female patients with PAI are often androgen-deficient. Male patients may have dehydroepiandrosterone values in the low to normal range. The significance of decreased serum dehydroepiandrosterone concentrations is yet to be determined; however, negative effects on mood, sense of well-being, and libido have been reported (Lang 2015). Dehydroepiandrosterone should be reserved for patients with PAI or SAI who continue to have impaired well-being despite adequate glucocorticoid replacement therapy (Arlt 2003). Despite weak evidence, the Endocrine Society guidelines for PAI recommend a 6-month trial of dehydroepiandrosterone replacement in premenopausal female patients with PAI who continue to have low energy concentrations, decreased libido, and/or depressive symptoms despite adequate glucocorticoid and mineralocorticoid replacement (Bernstein 2016). The typical replacement dosage is dehydroepiandrosterone 25–50 mg once daily each morning. If the patient does not have sustained symptom improvement within 6 months, dehydroepiandrosterone should be discontinued. If signs of over-replacement occur, such as increased hair growth or acne, the dehydroepiandrosterone dose should be reduced by 50% (Hahner 2009). Patients taking dehydroepiandrosterone should be monitored for improvement in energy concentrations and sense of well-being as well as sexual function. These can be managed by decreasing the dehydroepiandrosterone dose or frequency of administration. Morning serum dehydroepiandrosterone concentrations may be monitored periodically before taking the morning dose and should remain within the normal range for that patient's age group (Lang 2015).

Adrenal Crisis

Patients in adrenal crisis should be given bolus doses of normal saline as needed to maintain blood pressure. Initially, dosages as high as 1 L/hour may be necessary, and the patient should receive continuous cardiac monitoring (Bornstein 2016; Arlt 2003). If the patient is unresponsive to fluid resuscitation, a vasopressor may be added, though patients presenting with adrenal crisis as a result of PAI often have blunted responses to vasopressor therapy because of the concomitant decrease in mineralocorticoid (Arlt 2003). The Surviving Sepsis Campaign recommends intravenous hydrocortisone by continuous infusion administered equaling a total daily dose of 200 mg in

patients for whom hemodynamic stability cannot be obtained with fluid resuscitation and vasopressor treatment alone. Although clinical trial data are conflicting and the guideline recommendations weak, hydrocortisone use appears potentially beneficial, particularly in patients who may have underlying, undiagnosed adrenal insufficiency (Dellinger 2013).

HYPERFUNCTION OF THE ADRENAL GLAND

Cushing syndrome, primary hyperaldosteronism, pheochromocytoma, and adrenal tumors are four conditions that can result from hyperfunctioning of the adrenal gland. The next sections will cover Cushing syndrome and primary hyperaldosteronism.

Cushing Syndrome

Epidemiology/Etiology

Cushing syndrome refers to the development of signs and symptoms caused by exposure to supraphysiologic dosages of cortisol. The most common reason for inappropriately high cortisol concentrations is the exogenous administration of corticosteroids. Cushing disease, a form of Cushing syndrome, may also arise from the endogenous overproduction of glucocorticoids by the adrenal gland, which can be classified as either ACTH-dependent or ACTH-independent Cushing syndrome. About 80% of ACTH-dependent Cushing cases are the result of direct overproduction of ACTH by the pituitary gland. Chronic stimulation of the adrenal gland by ACTH results in bilateral adrenal hyperplasia. Other potential causes of ACTH-dependent Cushing syndrome are ectopic ACTH secretion from tumors and oversecretion of CRH. The remaining 20% of cases are the result of ACTH-independent Cushing syndrome. Most of these cases are the result of adrenal adenomas or adrenal carcinomas. In addition, the circadian rhythm that is precisely followed under normal conditions is lost in a patient with Cushing syndrome.

Given the rarity of the condition together with the clinical features it shares with type 2 diabetes, polycystic ovarian syndrome, and the metabolic syndrome, it is challenging to precisely determine the incidence and prevalence rates. Projected ranges are estimated to be 5–25 million people/year, though reported rates are much lower, with an estimated 2–3 million people/year with Cushing syndrome. Three times more women than men have Cushing syndrome, the reason for which is unknown (Steffensen 2010). Most women are affected at 25–45 years of age. Children may also have Cushing syndrome, with most cases occurring after puberty.

Symptoms/Clinical Presentation

The most common features of Cushing syndrome, occurring in about 90% of patients, are facial rounding and progressive central obesity. Fat accumulation typically occurs in the face, neck, trunk, and abdomen, whereas the extremities may experience wasting. The facial accumulation of fat leads to facial rounding, especially when deposited in the temporal fossae. When fat accumulates in the cheeks, "moon face" is often the characteristic feature that develops. A "buffalo hump" or a dorsocervical fat pad typically develops with weight gain and is noted in obesity. The presence of enlarged supraclavicular fat pads is a specific sign associated with Cushing syndrome. As a result, these supraclavicular fat pads often cause the patient's neck to appear short and thickened. If fat accumulates around the eyes, exophthalmos may occur, which develops in about 5% of patients with Cushing syndrome.

Dermatologic manifestations are prominent in patients with Cushing syndrome. The thinning of the stratum corneum leads to skin atrophy, especially in the extremities. Blood vessels may be more noticeable, and using adhesive tapes may cause the skin to peel off with removal. Women and older individuals may be more prone to skin atrophy because they have overall thinner skin than men and younger individuals. Because of glucocorticoid's detrimental effects on skin and tissue, a loss of connective tissue in the skin may cause the patient to bruise more easily. Wide purple striae, often greater than 1 cm, may develop as the skin expands. These marks often appear in areas such as the trunk, breasts, abdomen, buttocks, hips, upper thighs, and upper arms and appear reddish purple because of the inability of the atrophied skin to hide the coloration of the venous blood in the dermis. Because ACTH is the primary pigmentary hormone, patients with elevated ACTH secretion may have hyperpigmentation, particularly on areas of the body that are exposed to light such as the face, neck, hands, and legs and on areas prone to friction or pressure such as the elbows, knees, and waist.

Women often note changes in their menstrual cycles. This may be the result of negative feedback on gonadotropin-releasing hormone by excessive cortisol concentrations. Because the main source of androgens in women are the adrenal glands, women with hyperfunction of these glands may have hirsutism and acne.

Hypertension is a prominent finding in about 80% of adult and 47% of pediatric patients with Cushing syndrome (Cicala 2010). Although hypertension is usually mild to moderate, 17% may be considered severe. A significant correlation exists between hypertension and the duration of hypercortisolism, and there may be a link between the severity and cause of hypercortisolism. Development of hypertension in Cushing syndrome may result from the mineralocorticoid activity of cortisol, activation of the renin-angiotensin-aldosterone system, suppression of vasodilation, and enhanced sensitivity of β receptors to catecholamines caused by up-regulation of the sympathetic nervous system. In addition, increased cardiovascular reactivity to vasoconstrictors such as endothelin, increased cardiac output, total peripheral resistance, or renovascular resistance may be involved. Excessive cortisol concentrations lead to endothelial damage and enhance vascular permeability. Sleep apnea and insulin resistance may also be contributory.

Hypercortisolism also promotes gluconeogenesis, leading to glucose intolerance, and obesity, resulting in possible insulin resistance. Hyperglycemia is present in about 10%–15% of patients with Cushing syndrome and is more common in patients with a family history of type 2 diabetes. Control of excessive cortisol concentrations often leads to normalization of glucose concentrations.

Hypertension, obesity, and glucose intolerance collectively increase the patient's risk of cardiovascular disease. Hypokalemia is often a characteristic finding because cortisol mimics aldosterone, leading to actions on the sodium/potassium pump. Patients with Cushing syndrome are at an increased risk of venous thromboembolism (VTE). A systematic review determined a 1.9%–2.5% risk of VTE not caused by surgical procedures. Postoperatively, this risk was 0%–5.6%, with an outlier of 20%. High concentrations of factor VIII, factor IX, and von Willebrand factor as well as increased generation of thrombin as the result of excessive glucocorticoid concentrations potentially contribute to a hypercoagulable state (van Zaane 2009).

Hypercortisolism may also cause psychiatric symptoms, noted in about half of patients with Cushing syndrome. Emotional lability, depression, irritability, anxiety, and panic attacks may occur. Cognitive impairment, including learning and memory, may also result from high cortisol concentrations.

Infection, especially with opportunistic pathogens, is a concern. Severe infections have been detected in patients with a serum cortisol concentration of 43.1 mcg/dL, urinary cortisol excretion concentration greater than 2000 mcg/day, or urinary 17-hydroxycorticosteroid excretion greater than 35 mg/g of creatinine. In a small cohort of patients, 19 of 54 patients with Cushing syndrome had a severe infection and/or sepsis. Of these, bacterial infections were most common (73.7%). Opportunistic infections occurred in 42.1% of patients, and 13.8% of patients had infection with both bacterial and opportunistic pathogens (Sarlis 2000).

Symptom severity is patient-specific and depends on the degree and duration of elevated cortisol concentrations, presence or absence of coexistent androgen hypersecretion, etiology of Cushing syndrome, and patient age. Patients older than 50 may have milder symptoms than patients who present at a younger age.

Diagnostics

Initial Testing

Iatrogenic Cushing syndrome, arising from the exogenous use of corticosteroids, is the most common presentation. A thorough medical and drug history as well as a physical examination should be done before extensive laboratory testing. The Endocrine Society recommends testing for Cushing syndrome in the following four patient groups: those with unusual features for the patient's age such as the presence of hypertension or osteoporosis in a younger patient, patients with several features consistent with Cushing syndrome, children with increasing weight and decreasing height, and patients with the presence of adrenal tumors incidentally discovered but consistent with adenoma (Nieman 2008). In a patient with suspected hypercortisolism after excluding exogenous administration of corticosteroids as the causative factor, the first step is to determine the presence of excessive cortisol concentrations, which can be collected in the urine, serum, or saliva. This can be measured with one of the following tests: 24-hour urinary free cortisol (UFC) concentrations (two measurements), late-night salivary cortisol concentrations (two measurements), 1-mg overnight dexamethasone suppression test (DST), or longer low-dose DST (2 mg/day for 48 hours). Figure 1-4 provides an algorithm for the diagnostic workup of a patient with suspected Cushing syndrome.

Normal UFC concentrations are 20–90 mcg/24 hours, and their assessment is the most helpful urinary measurement in a patient with suspected Cushing syndrome. Elevated UFC concentrations, especially those greater than 4 times the upper limit of normal, are suggestive of Cushing syndrome, particularly when they are repeated as confirmation. Factors such as starvation, stress, overhydration (i.e., greater than 5 L/day), alcoholism, and drugs such as carbamazepine, topical corticosteroids, and fenofibrate can increase urinary cortisol concentrations. Patients with a GFR less than 20 mL/minute/1.73 m^2 may have a normal UFC concentration, despite the presence of excessive cortisol production, because urinary cortisol excretion is decreased in this patient population. Two measurements are suggested because of the variability in the concentration of hypercortisolism in Cushing syndrome. Although this measurement is valuable for the diagnostic workup of a patient with suspected Cushing syndrome, collecting urine over 24 hours is a challenge in some patients. The reported sensitivity for this test is 95% with a specificity of 98% (Kirk 2000).

Salivary cortisol concentrations significantly correlate with free cortisol concentrations in blood. In addition, the salivary concentrations of cortisol are not affected by the rate of salivary production. Patients collect saliva between 11:00 p.m. and midnight through passive drooling into a tube or by chewing on a cotton pledget for 1–2 minutes. The sample can be kept at room temperature or refrigerated for several weeks before it is analyzed. Accuracy, convenience, and reproducibility make salivary cortisol concentrations an acceptable alternative to UFC measurement. Patients using licorice or chewing tobacco and patients who smoke may have falsely elevated salivary cortisol concentrations because these agents contain glycyrrhizic acid, an inhibitor of an enzyme that converts active cortisol to inactive cortisone, thereby increasing concentrations. Ideally, patients should not smoke on the day of salivary collection, though the duration of this enzyme inhibition is unknown. Salivary measurement may not be the best option for nightshift workers or those with extremely variable bedtimes because this test is based on the nadir of cortisol during the late evening and early morning

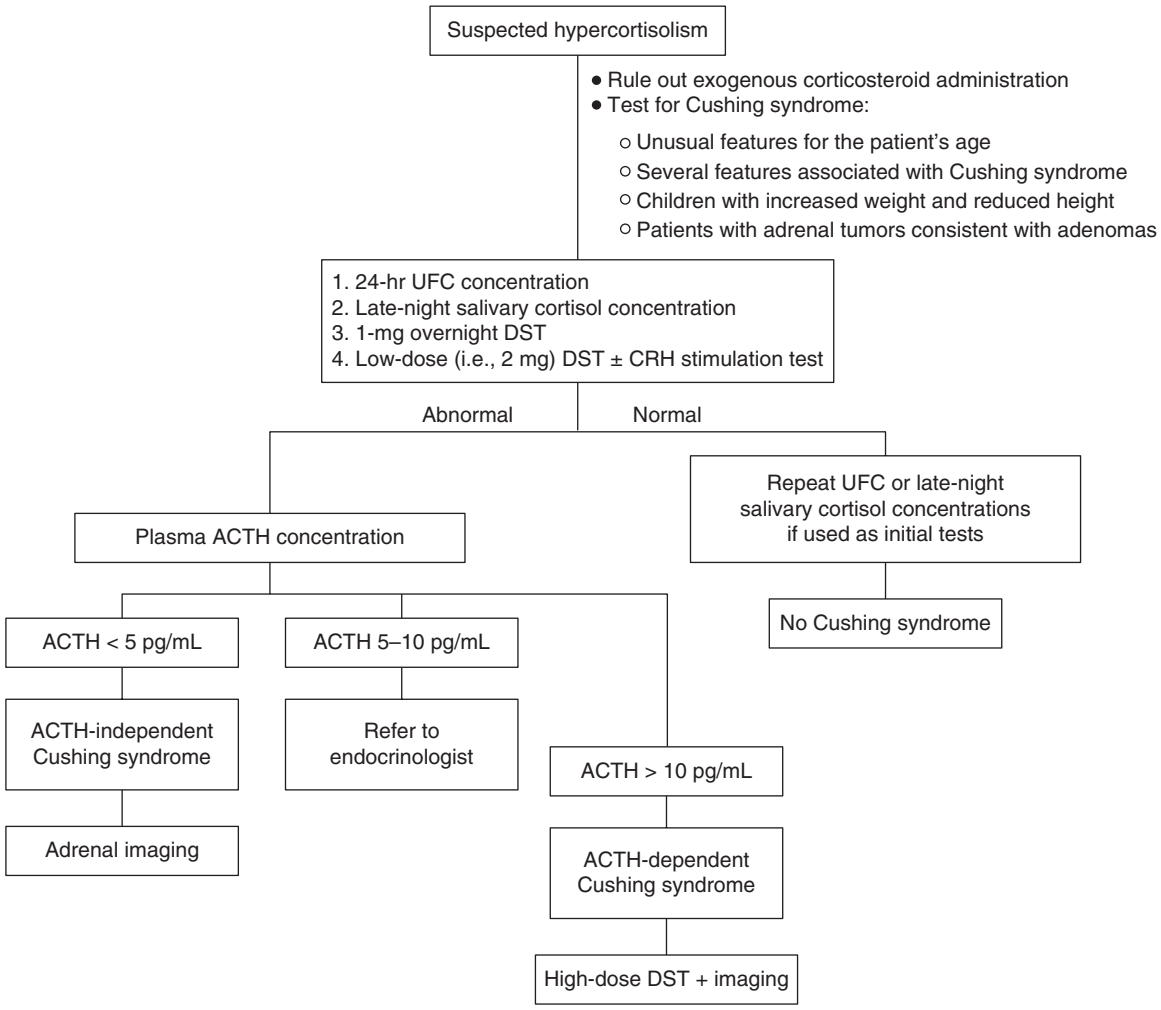

Figure 1-4. Diagnostic algorithm for suspected Cushing syndrome.

Note: Pregnant women and patients using certain anticonvulsants should receive special consideration.

DST = dexamethasone suppression test; UFC = urinary free cortisol.

Information from: Nieman LK, Biller BMK, Findling JW, Newell-Price J, et al. The diagnosis of Cushing's syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2008;93:1526-40.

hours. It should also be collected when the patient is not stressed and preferably in a calm, quiet environment.

Another test that may be used to assess Cushing syndrome is the 1-mg overnight DST. In a patient with Cushing syndrome attributable to an endogenous cause, a low dose of a glucocorticoid would fail to suppress ACTH and cortisol secretion. Patients take 1 mg of dexamethasone between 11:00 p.m. and midnight with subsequent measurement of cortisol concentrations between 8:00 a.m. and 9:00 a.m. the next day. A normal cortisol concentration after suppression by 1 mg of dexamethasone should be less than 5 mcg/dL. Therefore, a patient with Cushing syndrome is expected to have much higher concentrations. Some patients with Cushing syndrome can suppress even low-dose dexamethasone, so the Endocrine Society recommends a lower cutoff of less than 1.8 mcg/dL (Nieman 2008).

The longer low-dose DST is another measurement that may be considered as an initial step in diagnosing Cushing syndrome. This measurement may be more useful in patients with psychiatric conditions such as depression, anxiety, obsessive-compulsive disorder, obesity, alcoholism, and diabetes mellitus. Patients with these conditions have an overly active HPA axis without necessarily having Cushing syndrome. In general, this test has improved specificity compared with the 1-mg DST. According to the available data, this test has similar to slightly less diagnostic accuracy than the other tests. Patients are given 0.5 mg for 48 hours (totaling 2 mg/day), beginning at 9:00 a.m. and administered every 6 hours. The cortisol concentration is

measured at 9:00 a.m., 6 hours after the last dexamethasone dose. A serum cortisol concentration greater than 7.5 mcg/dL (or greater than 1.8 mcg/dL if the patient is sleeping) is suggestive of Cushing syndrome. In some cases, a combined CRH stimulation test will be included to increase the sensitivity of the tool. Once the longer low-dose DST is administered for 48 hours, CRH can be given as 1 mcg/kg intravenously 2 hours after the last dexamethasone dose, with the cortisol concentration assessed 15 minutes later. Adding CRH is expected to increase ACTH and cortisol secretion in patients with Cushing syndrome. This is particularly useful in the patient subset with Cushing syndrome having suppression in cortisol concentrations with DST testing (Nieman 2008).

For patients who have normal results from one of the four initial tests and who also have clinical features suggestive of Cushing syndrome, follow-up with an endocrinologist is warranted. Further evaluation is warranted in patients with at least one abnormal finding from the initial assessment.

Initial Testing in Special Populations

Corticosteroid-binding globulin concentrations are increased in patients who are pregnant or taking estrogen-containing products. Because the assays measure total cortisol, as many as 50% of women taking oral contraceptives have reported false-positive results for the DST test. Therefore, women should discontinue any estrogen-containing products for 6 weeks before testing in this manner, or more conveniently, the UFC measurement should be used in these patients. In pregnant women, UFC concentrations must be cautiously interpreted. During the first trimester, excretion of UFC is normal; however, UFC excretion increases 3-fold during the second and third trimesters to the same values as in nonpregnant women with Cushing syndrome. Therefore, only values exceeding this 3-fold increase can be considered diagnostic of Cushing syndrome in these patients.

Patients taking anticonvulsants such as carbamazepine, phenytoin, and phenobarbital may have false-positive results with DST testing. These anticonvulsants are inducers of the isoenzyme 3A4, which enhances the hepatic clearance of dexamethasone. Alternative testing such as the midnight salivary measurement should be considered in these patients.

Subsequent Testing

Once hypercortisolism has been diagnosed, the underlying etiology should be determined, particularly if the condition is ACTH-dependent or ACTH-independent. The plasma ACTH concentration should be assessed in late afternoon, generally after 4:00 p.m., when ACTH concentrations reach a nadir. An ACTH concentration of less than 5 pg/mL suggests ACTH-independent Cushing syndrome because cortisol overproduction suppresses the ACTH concentration. Plasma ACTH concentrations greater than 10 pg/mL indicate ACTH-dependent Cushing syndrome. Concentrations falling in the middle should be further assessed with a CRH stimulation test and referral to an endocrinologist.

In ACTH-independent hypercortisolism, an adrenal adenoma is usually the source, although some rare cases of micronodular and macronodular hyperplasia have been noted, and the focus shifts to adrenal imaging. Specifically, abdominal CT scanning or MRI is useful for visualizing the nodules and/or tumors.

Cushing disease; ectopic ACTH syndrome, particularly when the ACTH concentrations are extremely exaggerated; and ectopic CRH syndrome are typically the cause of ACTH-dependent hypercortisolism. Cushing disease is a form of Cushing syndrome in which the pituitary gland overproduces ACTH. For patients with suspected ACTH-dependent disease, high-dose DST assessment in combination with MRI studies is beneficial in locating the site of overproduction. The high-dose DST assessment is useful to distinguish between Cushing disease and ectopic ACTH production. Patients take 2 mg of dexamethasone every 6 hours for 48 hours total. During the last 24 hours of dexamethasone administration, a 24-hour urine collection is obtained. A positive result occurs when the UFC excretion is suppressed by 90% from baseline or if 17-hydroxysteroid excretion is suppressed by 64% (Kirk 2000).

Treatment

In patients with confirmed Cushing syndrome, the source of hypercortisolism should be removed. Surgical resection of primary lesions associated with Cushing disease and ectopic and adrenal cancer, adenoma, and bilateral disease remains the recommended initial treatment strategy for patients with ACTH-dependent and ACTH-independent Cushing syndrome unless they are not candidates for surgery. The Endocrine Society recommends transsphenoidal selective adenomectomy (TSS) as the initial surgical procedure for patients with Cushing disease (Nieman 2015). After the procedure, serum sodium concentrations should be assessed often for 5–14 days because transient diabetes insipidus and hyponatremia may occur. Hyponatremia occurs in about 5%–10% of patients and is more common in menstruating women undergoing more intensive exploration. Hemorrhaging and meningitis are also postoperative concerns. Free thyroxine concentrations should be assessed within 1–2 weeks postoperatively to identify any patients with subsequent hypothyroidism, which would necessitate treatment. Prolactin concentrations should also be assessed within 1–2 weeks after surgery to evaluate for hypopituitarism. Cortisol concentrations should also be evaluated if hypocortisolism needs to be treated. Because patients with Cushing disease are at risk of VTE, risk factors for this should be assessed, and perioperative prophylaxis is recommended (Nieman 2015).

In patients with evidence of incomplete resection of tumors or lesions, a repeat TSS is recommended. For patients

Table 1-1. Pharmacotherapy for Cushing Syndrome

Drug	Mechanism of Action	Dose	Adverse Effects
Adrenal Gland–Directed Drugs			
Etomidate	Steroidogenesis inhibitor, adrenostatic agent	0.3 mg/kg/hr IV	Venous pain, involuntary muscle movement, blood pressure abnormalities, arrhythmias
Ketoconazole	Steroidogenesis inhibitor, adrenostatic agent	0.4–1.6 g/day PO, divided three or four times per day	Gynecomastia, decreased libido, hepatotoxicity, abdominal discomfort, dermatologic manifestations
Metyrapone	Steroidogenesis inhibitor, adrenostatic agent	0.5–2 g/day PO, divided two to four times per day	Acne, hirsutism, hypertension, electrolyte imbalance, nausea, vomiting, headache, dizziness
Mitotane	Adrenolytic agent	0.25–0.8 g/day PO, divided three or four times per day	Nausea, diarrhea, lethargy, somnolence, gynecomastia, hyperlipidemia, vertigo, depression, hypocortisolism, prolonged bleeding time, teratogenic effects
Pituitary Gland–Directed Drugs			
Cabergoline	Dopamine receptor D_2 agonist	0.5–7 mg/wk PO	Cardiac valve disease, nausea, constipation, headache, dizziness
Pasireotide	Somatostatin analog	0.3–0.9 mg SC, twice daily	Diarrhea, nausea, hyperglycemia/diabetes, cholelithiasis, headache, abdominal pain, fatigue
Glucocorticoid Receptor Antagonists			
Mifepristone	Progesterone and glucocorticoid receptor antagonist	300–1200 mg/day, PO	Fatigue, nausea, vomiting, arthralgias, headache, hypertension, hypokalemia, edema, endometrial thickening

IV = intravenous(ly); PO = oral(ly); SC = subcutaneous(ly).

whose condition does not respond, patients with recurrent Cushing disease, or those who cannot tolerate surgery or in patients for whom the tumor is inoperable, radiation therapy is recommended. Radiation therapy has been associated with remission in up to 83% of adult patients (Nieman 2015) 6–60 months after treatment. Hypopituitarism is common after radiation therapy, and evaluation of pituitary function is warranted at least annually.

Drugs are rarely used as monotherapy in patients with Cushing syndrome and are generally indicated for pre- or postoperative use in patients awaiting a response. A systematic review found that drug therapy for the treatment of Cushing disease has little evidence to support it (Gadelha 2014). Drug therapy may be useful in patients who are not candidates for surgery or in those with persistent hypercortisolism. Selection of drugs are often driven by patient comorbidities, drug-drug interactions, and/or adverse effects. Table 1-1 lists drugs used in patients with Cushing syndrome.

Adrenal Gland–Directed Drugs

Metyrapone

Steroidogenesis inhibitors include ketoconazole, etomidate, and metyrapone. These may be useful in patients with Cushing syndrome by blocking the production of cortisol by the adrenal gland. Through blockage of 11-β-hydroxylase, metyrapone can quickly reduce (i.e., within 4 hours) cortisol

concentrations. Steroid synthesis is shifted toward androgen production; therefore, patients may develop acne and hirsutism. Metyrapone inhibits aldosterone synthesis; however, 11-desoxycorticosterone is produced, which exerts mineralocorticoid activity. As such, blood pressure and electrolyte abnormalities may occur with treatment. Patients may also have nausea, vomiting, headache, and dizziness with metyrapone. Currently, metyrapone is only available in the United States through a compassionate use program.

Ketoconazole

Unlike the quick onset of effects with metyrapone, ketoconazole has a delayed efficacy, with effects taking a few weeks to emerge. Ketoconazole inhibits both the 11- and 17-β-hydroxylase enzymes as well as several CYP isoenzymes. As such, gynecomastia and reduced libido may develop in men. Monitoring of liver function is warranted in patients receiving ketoconazole, given that it can increase liver enzyme concentrations. Because the drug affects the CYP system, several drug-drug interactions may occur and will require patient education about the concomitant use of other drugs.

Etomidate

Etomidate is rarely used except in urgent cases of hypercortisolism such as those accompanied by severe psychosis or sepsis. It is available only in an intravenous formulation and has significant adverse effects associated with its use.

Mitotane

Mitotane exerts cytotoxic effects on the adrenal cortex. Cells within the zona fasciculata and zona reticularis are degenerated, leading to atrophy of the adrenal cortex. According to the package insert, mitotane has a prolonged half-life of 18–159 days (median 53 days) and is distributed predominantly into fat. As a result, its onset of action is delayed, and therapy for around 6 months is needed for the UFC to normalize.

Mitotane is an adjunctive therapy in patients with Cushing disease with unsuccessful TSS who are awaiting the effects of pituitary radiation or in those who are not surgical candidates (Nieman 2015). Most patients receiving mitotane for this indication will have sustained cortisol suppression, with one study showing 72% of patients achieving complete remission with a median of 6 months of mitotane treatment (Baudry 2012).

Patients taking mitotane have adverse effects such as nausea, vomiting, and diarrhea. They have also reported lethargy, somnolence, and other CNS effects. One study reported that 28% of patients receiving mitotane discontinued treatment because of adverse effects (Baudry 2012). Mitotane, which is teratogenic, should not be administered to any woman who is pregnant or desires to become pregnant in the near future. Given the drug's long half-life, women should be advised against pregnancy for 2–3 years on discontinuation. Plasma measurements of mitotane can be used as a means of drug detection in the body.

Mitotane increases the production of corticosteroid-binding globulin. Therefore, monitoring of UFC or salivary cortisol measurements should occur. Hydrocortisone replacement doses should be increased by one-third in patients who develop adrenal insufficiency because mitotane is an inducer of CYP3A4. Subsequently, dexamethasone, another strong CYP3A4 inducer, should not be used in this patient population. Mineralocorticoid replacement is generally not required because mitotane used for short periods has minimal effects on the zona glomerulosa.

Pituitary Gland–Directed Drugs

Neurotransmitters such as acetylcholine, serotonin, γ-aminobutyric acid, and dopamine modulate pituitary secretion of ACTH. Cabergoline, a dopamine agonist, and pasireotide, a somatostatin analog, inhibit ACTH production.

Cabergoline exerts its action through activating D2 receptors in pituitary adenomas, thereby causing an inhibitory effect. In a study of 30 patients, cabergoline resulted in complete remission in 36.6% of patients and partial remission of 13.3% patients after 3–6 months of therapy. Thirty percent remained in complete remission after a mean of 37 months (range 12–60 months) with a mean dose of 2.1 mg/week (Godbout 2010). Adverse effects with cabergoline are related to increasing dopamine concentrations and include nausea, constipation, and dizziness. Concerns about cardiac valvular disease, particularly with dosages of 3–7 mg/week, have been raised, although these data are from patients using cabergoline for Parkinson disease (Pivonello 2015). A case report showed that cabergoline was safely used to treat hypercortisolism during pregnancy with no impact on the mother or the fetus (Woo 2013).

Combining cabergoline with other drugs has shown efficacy in small studies. Cabergoline monotherapy, at dosages of 2–3 mg/week, normalized UFC after 6 months of therapy in 3 of 12 patients with Cushing disease. In the nine nonresponders, adding ketoconazole in dosages of 200–400 mg/day normalized UFC in six patients, suggesting a potential benefit with combination therapy (Vilar 2010). In another study of 17 patients with Cushing disease who were receiving pasireotide, UFC was normalized in five patients (29%) with monotherapy. Adding cabergoline dosed with a taper of 0.5–1.5 mg every other day at day 28 normalized the UFC in four additional patients. At day 60, the eight remaining patients with elevated UFC received ketoconazole 200 mg orally three times daily, and six patients achieved remission. The overall response rate at the end of the study was 88% (Feelders 2010).

Pasireotide is a somatostatin analog that binds with high affinity to the somatostatin receptor (SSTR) subtype 5, which is overexpressed in corticotroph tumors. This causes activation of the SSTR to inhibit ACTH secretion, ultimately reducing the cortisol secretion, with maximum effects on UFC 2 months after treatment initiation. According to the package insert, pasireotide also has affinity for the SSTR 1, 2, and 3 subtypes. In a phase III clinical trial, 162 patients with Cushing

disease were randomized to receive 600 mcg or 900 mcg of pasireotide subcutaneously twice daily. After 3 months of treatment, those with UFC not exceeding 2 times the upper limit of normal continued with their doses; all others received an additional 300 mcg twice daily. The primary end point of normalization of UFC at 6 months without an increase in dose was achieved in 14.6% of patients receiving 600 mcg and in 26.3% of patients receiving 900 mcg of pasireotide. Normalization of UFC was achieved more commonly in patients with baseline UFC concentrations that did not exceed 5 times the upper limit of normal (Colao 2012).

The package insert states that the adverse effects reported in at least 20% of patients receiving pasireotide included diarrhea, nausea, hyperglycemia, diabetes mellitus, cholelithiasis, headache, abdominal pain, and fatigue. As such, monitoring of fasting plasma glucose or A1C is warranted at baseline and should be completed every week for the first 2–3 months and then periodically. Glucose should also be assessed for the first 2–4 weeks after any dosage increase. Hypokalemia and hypomagnesemia should be assessed and corrected, and an ECG should be done before initiating pasireotide because of concerns for bradycardia and QTc prolongation. Thyroid function should be measured to monitor pituitary function, and a gallbladder ultrasound should be done at baseline and then every 6 months because of the risk of cholelithiasis. Monitoring of liver function tests should also be done at baseline, followed by 1–2 weeks after initiation, monthly for 3 months, and then every 6 months (Pivonello 2015).

Glucocorticoid Receptor Antagonists

Glucocorticoid receptor antagonists work quickly to control excessive cortisol concentrations. Mifepristone has a labeled indication for the treatment of hyperglycemia in patients with Cushing syndrome associated with diabetes or glucose intolerance who are either not candidates for surgery or did not respond to surgery (Nieman 2015).

Mifepristone is a nonselective antagonist of the glucocorticoid receptor type II, causing increases in ACTH and cortisol concentrations. Hypercortisolism may lead to activation of the mineralocorticoid receptor, causing subsequent hypertension, hypokalemia, edema, and alkalosis. Aldosterone antagonists (AAs) may be warranted to treat these symptoms. Fatigue, nausea, vomiting, arthralgias, and headache may occur as a result of cortisol insufficiency. Women may have endometrial thickening because of mifepristone's antiprogestin effects. Mifepristone, which is an abortifacient, should not be used in pregnant women or in women wishing to become pregnant.

The effects of mifepristone on glucose AUC and diastolic blood pressure were assessed in a study of 50 patients with Cushing syndrome with either type 2 diabetes/glucose intolerance or hypertension. In the diabetes cohort, the AUC for glucose improved in 60% of patients ($p<0.0001$). In the hypertension cohort, diastolic blood pressure readings improved in 38% of patients ($p<0.05$). An overall response rate of improvement in clinical status occurred in 87% of patients ($p<0.0001$) (Fleseriu 2012).

Hyperaldosteronism

Excessive aldosterone concentrations are collectively called "hyperaldosteronism." When these excessive concentrations are result of overstimulation of the adrenal gland, they are called "primary hyperaldosteronism." When the overproduction is caused by stimulation from a source outside the adrenal gland, they are called "secondary hyperaldosteronism."

Etiology/Epidemiology

Primary hyperaldosteronism is the most common cause of secondary hypertension, with an estimated prevalence of 5%–20% (Fagugli 2011). In the Primary Aldosteronism Prevalence in Hypertensives study, the overall prevalence of primary aldosteronism was 11.2% of 1125 patients with newly diagnosed hypertension, with 4.8% of the patients having aldosterone-producing adenoma as the cause (Rossi 2006). The Endocrine Society suggests that primary hyperaldosteronism is a group of disorders characterized by excessive aldosterone concentrations that cannot be suppressed by sodium loading. The hyperaldosteronism is minimally, if at all, attributed to angiotensin II and potassium concentrations (Funder 2016).

Reduced renal blood flow from renal artery stenosis, heart failure, and cirrhosis stimulates the renin-angiotensin-aldosterone system to overproduce aldosterone, leading to secondary hyperaldosteronism. Excessive intake of potassium; pregnancy; oral contraceptive use, especially oral contraceptives containing drospirenone; and menses may also result in excessive aldosterone production.

Symptoms/Clinical Presentation

Patients with primary or secondary hyperaldosteronism present with moderate to severe hypertension that is often resistant to several antihypertensives. Both hypokalemia and hypernatremia have occurred in patients with hyperaldosteronism. Hypokalemia may be more common in severe cases. Other symptoms include fatigue, muscle weakness, headache, numbness, episodic paralysis, polydipsia, and polyuria. More women than men have hyperaldosteronism, and symptoms typically emerge between the third and sixth decades of life.

Diagnostics

The Endocrine Society guidelines recommend screening individuals with stage 2 hypertension or resistant hypertension in patients receiving three or more antihypertensives together with the aldosterone-to-renin ratio (ARR) because it is a reliable screening tool for primary hyperaldosteronism. The ARR is a ratio of the plasma-aldosterone concentration (PAC) to the PRA in which the aldosterone concentration is divided by PRA. This helps the practitioner differentiate primary from secondary hyperaldosteronism. These concentrations

are ideally obtained mid-morning when the patient has been awake for at least 2 hours and sitting for at least 5–15 minutes. Before screening, potassium should be normalized, if warranted, and drugs that interfere with the renin-angiotensin-aldosterone system should be discontinued. An ARR greater than 30 when the PAC is greater than 15 ng/dL usually suggests primary hyperaldosteronism (Kumar 2014).

After a patient has a positive ARR screening test, the finding should be confirmed. The Endocrine Society acknowledges four testing procedures with no preference given to recommending one over another. Selection of confirmatory testing should be influenced by cost, patient adherence, and laboratory capabilities. An oral sodium loading test in which the patient ingests two 1-g tablets of sodium chloride three times daily for 3 days, or a saline infusion test in which a 500 mL/hour infusion of normal saline is administered over 4 hours, may be used. Sodium loading should normally suppress urine aldosterone concentrations to less than 10 mcg/24 hours or the PAC to less than 5 ng/dL. If the urine aldosterone concentration exceeds 12 mcg/24 hours, primary hyperaldosteronism is confirmed. Caution should be used in patients with uncontrolled hypertension and in those with heart failure when using sodium loading tests. Patients may also undergo fludrocortisone suppression testing (FST), in which they receive 0.1 mg of fludrocortisone orally every 6 hours for 4 days. A positive FST is defined as a PAC greater than 6 mg/dL with a PRA less than 1 ng/mL/hour and when the plasma cortisol concentration assessed on day 4 is less than the concentration obtained 7 hours prior. The captopril challenge involves patients receiving 25–50 mg of captopril. A positive result is a PAC elevation 1–2 hours after captopril administration (Funder 2016; Kumar 2014).

To treat hyperaldosteronism, imaging with an adrenal CT scan is recommended for subtyping a patient and ruling out adrenocortical carcinoma (Funder 2016). A CT scan detects masses greater than 2.5 cm; therefore, smaller masses or nonfunctioning macroadenomas may be not be identified. Adrenal vein sampling, a process to evaluate for the presence of hyperaldosteronism, may be used in combination with CT imaging to determine whether a patient's primary hyperaldosteronism is unilateral or bilateral. This is important because unilateral hyperaldosteronism can be surgically cured, whereas bilateral hyperaldosteronism is medically managed (Funder 2016).

One systematic review found that if CT/MRI imaging had been used exclusively to determine lateralization, 14.6% of patients would have inappropriately received an adrenalectomy because adrenal vein sampling revealed bilateral involvement warranting medical treatment. In addition, 19.1% of patients would not have received an adrenalectomy when, in fact, they were appropriate candidates with unilateral adrenal abnormality, and 3.9% of patients would have received an adrenalectomy on the wrong side because adrenal vein sampling found inappropriate excessive aldosterone excretion in the opposite side. This totals 37.8% of patients with a misdiagnosis with CT/MRI imaging alone (Kempers 2009). Limitations of adrenal vein sampling include cost, invasive procedures, and limited availability of procedure at health care facility.

Treatment

Unilateral primary hyperaldosteronism and hyperaldosteronism caused by an aldosterone-producing adenoma should be treated with laparoscopic adrenalectomy and resection of the adenoma, respectively. Most patients with unilateral primary aldosterone will have improvements in potassium concentrations and blood pressure readings. After an adrenalectomy in patients with aldosterone-producing adenomas, half will have normalization of blood pressure with no use of an antihypertensive agent (Funder 2016).

Patients with bilateral adrenal hyperplasia or those with unilateral adrenal hyperplasia or aldosterone-producing adenomas who do not undergo surgery are medically treated with AAs in the absence of contraindications. The Endocrine Society acknowledges spironolactone as the choice in the medical management of primary hyperaldosteronism because it has been associated with a 25% mean reduction in systolic blood pressure and a 22% mean reduction in diastolic blood pressure over 1–96 months with doses of 50–400 mg/day (Funder 2016). Because spironolactone is nonselective, adverse reactions such as menstrual irregularities and breast tenderness in women and impotence and gynecomastia in men may occur. Potassium concentrations, serum creatinine, and blood pressure should be monitored during the first 4–6 weeks of treatment and with any dosage adjustments, or sooner depending on clinical judgment, especially in patients with renal dysfunction.

Eplerenone is a selective aldosterone receptor antagonist, though hyperkalemia remains a concern. Patients generally initiate treatment with 25–50 mg orally once daily, increasing to 50 mg twice daily after 4–8 weeks. Eplerenone, a substrate for CYP3A4, should not be used with potent inhibitors of this isoenzyme. Patients taking moderate CYP3A4 inhibitors should start with 25 mg once daily. Monitoring values are similar to those for spironolactone. The antihypertensive effects of eplerenone and spironolactone were compared in a 16-week, double-blind study of patients with hypertension caused by primary hyperaldosteronism. In patients receiving eplerenone, the primary outcome of diastolic blood pressure readings decreased by –5.6 mm Hg (±1.3 mm Hg) compared with –12.5 mm Hg (±1.3 mm Hg) in those receiving spironolactone, resulting in a difference of –6.9 mm Hg (95% CI, –10.6 to –3.3; p=0.001). In patients receiving eplerenone, the secondary outcome of systolic blood pressure readings decreased by –9.9 mm Hg (±2.3 mm Hg) compared with -27.0 mm Hg (±2.3 mm Hg) for those receiving spironolactone, a difference of –17.1 mm Hg (95% CI, –23.4 to –10.8; p<0.001). More patients in the spironolactone group than in the eplerenone group had male gynecomastia (21.2% vs.

Patient Care Scenario

A 65-year-old white woman (height 62 inches, weight 87.3 kg [192 lb]) presents to the clinic with reports of extreme muscle weakness, increased thirst, and excessive urination. She thought it might be the result of longstanding, often erratically controlled diabetes mellitus; however, self-reported blood glucose monitoring reveals preprandial blood glucose concentrations within normal limits for the past 6 months. Her medical history is significant for type 2 diabetes, hypertension, dyslipidemia, and renal artery stenosis secondary to diabetes. Her blood pressure in the clinic is 178/98 mm Hg, heart rate 92 beats/minute, respiratory rate 20 breaths/minute, and current pain 0/10. Her laboratory test results include Na 148 mEq/L, K 3.6 mEq/L, Cl 100 mEq/L, BUN 16 mEq/L, SCr 2.3 mg/dL, calcium 9.8 mg/dL, magnesium 2.1 mg/dL, and fasting blood glucose 92 mg/dL. Diagnostic tests show an ARR of 40, PAC 22 ng/dL, and positive fludrocortisone suppression test (FST). Given these findings, she undergoes a CT scan, which confirms primary hyperaldosteronism, which is unilateral. What is the next step that should be taken for this patient?

ANSWER

Patient symptoms of muscle weakness, polyuria, and polydipsia, together with an elevated blood pressure and hypernatremia, are highly suggestive of hyperaldosteronism. As such, the appropriate diagnostic steps were taken. An ARR (a ratio of the PAC to the PRA) greater than 30 with a PAC greater than 15 ng/dL generally indicates primary hyperaldosteronism, which is true for this patient. After a positive ARR screening, a confirmatory test should be done. In this case, the patient tested positive with FST, for which she would have received 0.1 mg of fludrocortisone orally every 6 hours for 4 days. Finally, a CT scan of the adrenal gland is done to determine the subtype for the patient. In this case, it was determined to be unilateral adrenal hyperplasia, which is likely caused by renal artery stenosis. Reduced blood flow because of this condition can lead to aldosterone overproduction. Current guideline recommendations from the Endocrine Society suggest that patients with unilateral adrenal hyperplasia should undergo unilateral laparoscopic adrenalectomy. Therefore, this patient would be a candidate for surgery, barring any other concerns about surgical risks. If she is deemed not to be a candidate for surgery or elects not to undergo the procedure, second-line management would be therapy with an AA.

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2. Kempers MJE, Lenders JWM, van Outheusden L, et al. Systematic review: diagnostic procedures to differentiate unilateral from bilateral adrenal abnormality in primary aldosteronism. Ann Intern Med 2009;151:329-37.
3. Kumar B, Swee M. Aldosterone-renin ratio in the assessment of primary aldosteronism. JAMA 2014;312:184-5.

4.5%, p=0.033) and female breast pain (21.1% vs. 0%, p=0.023) (Parthasarathy 2011). This study suggests that spironolactone has a greater antihypertensive effect in patients with hypertension caused by primary hyperaldosteronism, at the expense of more adverse effects.

Amiloride is a potassium-sparing diuretic that may be useful to control blood pressure in patients with primary hyperaldosteronism. It is usually initiated at 5 mg orally twice daily and titrated to effect. However, it may need to be combined with low doses of a thiazide diuretic such as hydrochlorothiazide 12.5–25 mg once daily, especially if hypervolemia should be corrected to increase amiloride response.

In patients with familial hyperaldosteronism type I, also known as *glucocorticoid-remediable* hyperaldosteronism, synthetic glucocorticoid use is recommended to partly suppress ACTH secretion (Funder 2016). Patients can receive dexamethasone 0.125–0.25 mg orally once daily or prednisone 2.5–5 mg orally once daily administered at bedtime in order to target the early-morning surge of ACTH. If blood pressure is not normalized with glucocorticoid administration, use of an AA should be considered (Funder 2016).

Patients with secondary hyperaldosteronism should be treated according to etiology, with correction of the stimulation causing excessive production of aldosterone. Spironolactone may be useful in the interim until the etiology is determined.

MONITORING

Hypofunction

The treatment goal for a patient with hypofunction of the adrenal gland is to be able to perform activities of daily living with no limitations. This includes limiting fatigue, maintaining a good appetite and stable weight, and having normal sexual functioning. Monitoring for appropriate glucocorticoid replacement should include body weight, blood pressure, and energy concentrations as well as monitoring for signs of corticosteroid excess or insufficiency (Bornstein 2016; Arlt 2003). The provider should ask detailed questions about the patient's activities of daily living in order to ascertain the effectiveness of the current glucocorticoid replacement regimen. Chronic under-replacement may result in increased hyperpigmentation of the skin (Oksnes 2015). Patients should follow up with an endocrinologist at least once a year.

Patients with SAI caused by corticosteroid-induced HPA axis suppression should be monitored for recovery of the HPA axis. A monthly morning cortisol concentration before the patient's morning corticosteroid dose may be useful in

monitoring for HPA axis recovery. Once the cortisol concentration is greater than 10 mcg/dL, a standard-dose 250-mcg corticotropin stimulation test should be done to ensure full HPA axis recovery (Krasner 1999).

Monitoring for adequate mineralocorticoid replacement should include assessment of patient salt cravings, occurrence and frequency of postural hypotension or hypertension, and edema. Serum sodium and potassium should be monitored periodically to ensure they are within normal limits. Plasma-renin concentration may also help identify whether mineralocorticoid replacement is adequate. Serum concentrations should be at the upper end of the reference range (Hahner 2010). However, if signs and symptoms of over-replacement occur, the dosage of mineralocorticoid should be reduced, despite a PRA within the target range (Quinkler 2015).

Patients taking dehydroepiandrosterone should be monitored for improvement in energy concentrations and sense of well-being as well as sexual function. Signs of over-replacement should also be assessed, which most often include acne and increased hair growth. These can be managed by decreasing the dehydroepiandrosterone dose or frequency of administration. Morning serum dehydroepiandrosterone concentrations, before taking the morning dose, may be monitored periodically, and values should remain within the normal range for that patient's age group. In women, increased serum androgen concentrations may be monitored as well (Lang 2015).

Hyperfunction

Normalization of cortisol concentrations remains central to the treatment of patients with Cushing syndrome. In addition, managing the comorbidities associated with hypercortisolism is imperative (Nieman 2015). For patients with hyperaldosteronism, identifying the cause of the excessive aldosterone production together with appropriate management is warranted to minimize the cardiovascular and renal complications that might result.

Surgical interventions are often the preferred, first-line treatment in patients with over-functioning adrenal glands. In the pre- and postoperative setting as well as in patients who choose to be medically managed, blood pressure and electrolytes, particularly those that were abnormal with initial clinical presentation, should be closely monitored. In general, patients undergoing surgical interventions are followed closely within a few weeks of the intervention to determine the effects of the intervention on their blood pressure, electrolytes, and adrenal/pituitary functioning.

PATIENT EDUCATION

Patient education begins with a discussion of what their adrenal condition entails together with how it is best treated. Patients taking corticosteroids should be counseled to take them as prescribed each day and instructed that this medication will be a lifelong treatment for their PAI or SAI, except for glucocorticoid-induced adrenal insufficiency. Counseling should be provided regarding the signs and symptoms of both under- and over-replacement so that patients can report such symptoms to their provider for corticosteroid dose adjustment. Patients and their caregivers should be counseled regarding when and how to increase their corticosteroid dosage during stress or illness and receive regular reinforcement regarding appropriate management strategies.

Practice Points

Given the complexity of adrenal disorders, together with nonspecific clinical presentations in many cases, pharmacists often face challenges in the care of these patients. The following are key points to consider when providing medical care for a patient with an adrenal disorder:

- **PAI is characterized by decreased serum cortisol, decreased PRA, decreased serum aldosterone, and decreased dehydroepiandrosterone. The most common cause is autoimmune adrenalitis.**
- **SAI is characterized similarly to PAI; however, mineralocorticoid activity is preserved. The most common cause is withdrawal from long-term use of corticosteroids.**
- **The standard-dose corticotropin stimulation test is the initial diagnostic test of choice to establish a diagnosis of adrenal insufficiency.**
- **Hydrocortisone at a dose of 15–25 mg daily is the preferred initial drug for adrenal insufficiency.**
- **Patients with PAI will require fludrocortisone 50–100 mcg daily.**
- **Dehydroepiandrosterone may be initiated in patients with continued fatigue and decreased sense of well-being while receiving optimal glucocorticoid replacement therapy.**
- **Cushing disease is characterized by the development of signs and symptoms resulting from exposure to supraphysiologic doses of cortisol. The most common cause is exogenous administration of corticosteroids.**
- **Patients with Cushing syndrome may present with hypertension, moon face, buffalo hump, wide purple striae, and/or glucose intolerance.**
- **Initial testing for Cushing syndrome consists of measuring cortisol concentrations, which may occur through urine or saliva measurements or with the use of dexamethasone suppression. Subsequent testing is warranted in those with hypercortisolism to determine the etiology and involves measuring plasma ACTH concentrations.**
- **Drugs are rarely used as monotherapy in patients with Cushing syndrome and are usually indicated to be used pre- or postoperatively in patients awaiting a response.**
- **Patients with hyperaldosteronism often present with moderate to severe hypertension, hypo- or normokalemia, muscle weakness, and polydipsia.**
- **The ARR is the preferred screening tool in suspected hyperaldosteronism because it helps differentiate primary from secondary disease.**
- **Patients with bilateral adrenal hyperplasia or those with unilateral adrenal hyperplasia or aldosterone-producing adenomas who do not undergo surgery are treated with AAs in the absence of contraindications.**

They should also be made aware of the signs and symptoms of an adrenal crisis and informed that emergency care is necessary, should these occur. They should understand the importance of adequate calcium and vitamin D intake to help minimize deleterious effects on the bone. Pharmacists are not only positioned to help them in this preventive care but also to suggest appropriate screening for osteoporosis according to risk factors. If patients have vomiting or diarrhea, they should be instructed to contact their practitioner because the glucocorticoid may need to be given parenterally. In some cases, the patient may be prescribed an emergency glucocorticoid injection administration kit or hydrocortisone suppositories for use. All patients should either carry a corticosteroid emergency card or wear an emergency medical alert ID bracelet. Corticosteroid emergency cards are available online.

Patients with PAI receiving mineralocorticoid replacement therapy should be instructed not to restrict salt from their diets. However, patients should make sure the salt is sodium chloride and not a salt substitute such as potassium chloride because of the risk of hyperkalemia in these patients. Patients receiving mineralocorticoid replacement therapy should take these on a daily basis. Patients should monitor their salt cravings as well as their blood pressure for signs of over- or under-replacement. It has also been suggested that all patients be equipped with a parenteral emergency glucocorticoid administration kit (Arlt 2003).

For patients receiving medical management for hyperfunctioning of the adrenal gland, proper education regarding administration, adherence, adverse effects, and appropriate frequency of monitoring is critical for normalization of their conditions. Given that drugs such as ketoconazole and eplerenone work through the CYP system, screening for important drug-drug interactions can help ensure that patients are safely receiving therapy. Women receiving mitotane or mifepristone for Cushing syndrome should understand the importance of using contraception with an additional backup method while receiving treatment.

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Self-Assessment Questions

Questions 1 and 2 pertain to the following case.

T.M. is a 68-year-old woman who describes significant muscle weakness and fatigue for the past 3–4 months. She denies any changes in her concentration of physical activity or lifestyle. Her medical history is significant for gastroesophageal reflux disease (GERD) and alcoholic cirrhosis, which are treated with ranitidine 150 mg orally twice daily and vitamin E 400 international units orally once daily. Her vital signs today are blood pressure 178/96 mm Hg, heart rate 98 beats/minute, respiratory rate 22 breaths/minute, and pain 0/10. Her laboratory values are Na 147 mEq/L, K 3.1 mEq/L, Ca 10.6 mg/dL, SCr 1.1 mg/dL, AST 258 IU/L, ALT 156 IU/L, and albumin 3.3 g/dL.

1. Which area of the adrenal gland is most likely responsible for T.M.'s clinical presentation and initial laboratory data?

   A. Medulla
   B. Zona fasciculata
   C. Zona glomerulosa
   D. Zona reticularis

2. Which one of the following is the best diagnostic test to obtain first when assessing T.M. for an adrenal disorder?

   A. Aldosterone-to-renin ratio (ARR)
   B. Fludrocortisone suppression test (FST)
   C. Plasma adrenocorticotropic hormone (ACTH) concentration
   D. Salivary cortisol concentration

3. A 50-year-old woman (stable weight 76 kg [168 lb]) presents to the clinic with increased blood pressure over the past 3 months. Her home blood pressure log reveals the following values over the past 2 weeks: 162/94, 168/100, 156/96, 172/98, and 160/96 mm Hg. Her medical history is significant for primary adrenal insufficiency (PAI), for which she has received stable doses of hydrocortisone 25 mg orally daily and fludrocortisone 100 mcg daily for the past year. She has no other complaints at this time. Her vital signs today are blood pressure 174/97 mm Hg and heart rate 89 beats/minute. Her laboratory data are as follows: Na 144 mg/dL, K 5.0 mg/dL, Cl 106 mEq/L, BUN 14 mg/dL, SCr 1.1 mg/dL, calcium 8.2 mg/dL, magnesium 1.9 mEq/L, fasting blood glucose 92 mg/dL, and albumin 3.0 g/dL. Which one of the following is best to recommend for managing this patient's blood pressure?

   A. Decrease hydrocortisone dose to 15 mg daily.
   B. Decrease fludrocortisone dose to 75 mcg daily.
   C. Initiate dehydroepiandrosterone orally 25 mg daily.
   D. Initiate hydrochlorothiazide orally 25 mg daily.

4. A 29-year-old woman with Cushing syndrome continues to have hypertension, obesity, and glucose intolerance, despite a recent transsphenoidal selective adenomectomy (TSS). Today, her blood pressure is 176/96 mm Hg, heart rate 98 beats/minute, and fasting blood glucose 124 mg/dL. She currently takes ethinyl estradiol (30 mcg)/drospirenone (3 mg) orally once daily. Her laboratory data today are Na 138 mEq/L, K 5.2 mEq/L, Cl 101 mEq/L, BUN 14 mEq/L, SCr 1.0 mg/dL, calcium 8.36 mg/dL, magnesium 2.1 mg/dL, albumin 4.4 g/dL, and fasting blood glucose 83 mg/dL. She plans to become pregnant within the next year. Which one of the following is the best adjunctive therapy to recommend for this patient?

   A. Cabergoline; this drug may have negative effects on the heart, and she should report any palpitations or chest pain to a health care provider.
   B. Ketoconazole; the patient should take this medication at the same time daily; it will take several weeks to months to see improvements with this drug.
   C. Metyrapone; the patient should see improvements quickly with treatment.
   D. Mitotane; the patient should continue her oral contraceptive and consider a backup method such as a condom because this agent is contraindicated during pregnancy.

5. Which one of the following patient counseling points, if shared at each visit, is most likely to reduce the risk of hospitalization from an adrenal crisis?

   A. An increased daily corticosteroid dose may be warranted during acute illness.
   B. If signs and symptoms of adrenal crisis appear, double the oral corticosteroid dose until the symptoms resolve.
   C. Decrease the dose of corticosteroid during times of increased stress.
   D. Decrease the corticosteroid dose with symptoms of dizziness or hypotension.

6. A company is pursuing a new drug product to treat the androgenic effects associated with Cushing syndrome (e.g., menstrual irregularities, acne, hirsutism). Which one of the following drug types would most likely reduce these effects in a woman with Cushing syndrome?

   A. ACTH agonist
   B. Aldosterone antagonist (AA)
   C. Angiotensin III antagonist
   D. Gonadotropin-releasing hormone agonist

7. A 58-year-old man presents to the ED with signs and symptoms consistent with adrenal crisis. His medical history is significant for hypothyroidism, cirrhosis, and chronic low back pain. His current drugs include levothyroxine 125 mcg orally daily and meloxicam 15 mg orally daily. His vital signs are blood pressure 92/58 mm Hg and heart rate 68 beats/minute. Which one of the following is best to recommend as initial treatment of this patient's adrenal crisis?

   A. Normal saline intravenously 50 mL/hour
   B. Hydrocortisone 100 mg intravenous bolus
   C. Fludrocortisone 50 mcg orally daily
   D. Norepinephrine intravenously titrated as needed to maintain mean arterial pressure

8. A 36-year-old woman (height 65 inches, weight 91 kg [201 lb]) with moderate rheumatoid arthritis (RA) comes to the rheumatology clinic for her 6-month follow-up visit. Her RA is moderately managed with adalimumab 40 mg subcutaneously every other week, methotrexate 15 mg orally once a week, sulfasalazine 500 mg orally twice daily, folic acid 1 mg orally once daily, prednisone 20 mg orally once daily, meloxicam 15 mg orally once daily, and calcium 500 mg/vitamin D 400 international units orally once daily. The patient reports mild pain and swelling in her wrists. Physical examination reveals a "moon face" with significant thinning of the skin, especially on her arms and legs, in addition to bilateral swelling in her wrists. Her blood pressure is 140/86 mm Hg, heart rate 80 beats/minute, respiratory rate 20 breaths/minute, temperature 98.1°F (37°C), and pain score 3/10 in both wrists. Her laboratory values today are Na 141 mEq/L, K 4.5 mEq/L, Cl 100 mEq/L, BUN 15 mEq/L, SCr 1.2 mg/dL, calcium 9.6 mg/dL, magnesium 2.2 mg/dL, albumin 5.1 g/dL, and fasting blood glucose 131 mg/dL. A urinary free cortisol (UFC) concentration is 320 mcg/24 hours, plasma ACTH concentration 12 pg/mL, ARR 11, and plasma-aldosterone concentration (PAC) 5 ng/dL. Which one of the following adrenal disorders does this patient most likely have?

   A. ACTH-dependent Cushing syndrome
   B. ACTH-independent Cushing syndrome
   C. Primary hyperaldosteronism
   D. Secondary hyperaldosteronism

9. A 69-year-old man is prescribed mitotane 0.5 mg orally three times daily to manage Cushing disease. He has undergone three TSS procedures in the past and will receive radiation next week. Which one of the following statements regarding treatment with mitotane and subsequent monitoring is best to document in this patient's medical chart?

   A. Do not start treatment with mitotane; the patient should undergo surgical intervention with monitoring of cortisol concentrations.
   B. Start treatment with mitotane; closely monitor urinary free cortisol concentrations because normalization of concentrations is expected within about 6 months of initiation.
   C. Start treatment with mitotane; closely follow aldosterone concentrations because he will likely need to receive fludrocortisone therapy.
   D. Start treatment with mitotane; closely monitor salivary cortisol concentrations because dexamethasone will need to be administered if he develops adrenal insufficiency.

Questions 10 and 11 pertain to the following case.

M.K. is a 52-year-old man who reports increasing fatigue, dizziness, and weight loss over the past 6 months. He denies any significant changes to his lifestyle. His medical history is significant for dyslipidemia and allergic rhinitis; these are treated with atorvastatin 40 mg orally daily and cetirizine 10 mg orally once daily as needed. M.K.'s vital signs are blood pressure 110/68 mm Hg, heart rate 94 beats/minute, and weight 76 kg (168 lb; decreased 7 kg [15 lb] in the past 6 months). Laboratory values today are Na 134 mEq/L, K 5.3 mEq/L, Cl 102 mEq/L, BUN 18 mg/dL, SCr 1.6 mg/dL, calcium 9.9 mg/dL, magnesium 2.0 mEq/L, fasting blood glucose 86 mg/dL, and albumin 3.2 g/dL.

10. Which one of the following is the best initial diagnostic test to recommend for M.K.?

    A. Insulin-induced hypoglycemia
    B. Low-dose corticotropin stimulation
    C. Overnight metyrapone
    D. Standard-dose corticotropin stimulation

11. M.K. is given a diagnosis of adrenal insufficiency, and the physician wants to begin treatment with prednisolone. Which one of the following would most likely eliminate prednisolone as an initial treatment choice for M.K.?

    A. Higher mineralocorticoid effect
    B. Once-daily dosing
    C. Higher glucocorticoid potency
    D. Drug-drug interactions

12. A 33-year-old woman (height 67 inches, weight 97.5 kg [215 lb]) reports extreme fatigue with more frequent headaches during the past month. She attributes these symptoms to a recent change in jobs. She has feelings of "worthlessness" and cries "most days of the week" because she divorced her husband 3 months ago. Her blood pressure today is 150/96 mm Hg, heart rate 88 beats/minute, respiratory rate 22 breaths/minute, and current pain score 2/10 (headache). Her laboratory test

results today are Na 146 mEq/L, K 4.1 mEq/L, Cl 101 mEq/L, BUN 17 mEq/L, SCr 0.9 mg/dL, calcium 9.6 mg/dL, magnesium 2.0 mg/dL, albumin 4.9 g/dL, and fasting blood glucose 99 mg/dL. A 1-mg dexamethasone suppression test (DST) resulted in a cortisol concentration of 2 mcg/dL, ACTH 1.2 pg/mL, standard high-dose ACTH stimulation test 21 mcg/dL, ARR 48, and PAC 25 ng/dL. Which one of the following adrenal disorders does this patient most likely have?

A. Adrenal insufficiency
B. Cushing disease
C. Cushing syndrome
D. Hyperaldosteronism

13. A 36-year-old woman has been given a diagnosis of bilateral adrenal hyperplasia. In addition, she has dyslipidemia and seasonal allergic rhinitis. Her blood pressure today is 148/92 mm Hg, heart rate 82 beats/minute, respiratory rate 21 breaths/minute, and pain score 0/10. Her laboratory test results today are Na 137 mEq/L, K 4.8 mEq/L, Cl 99 mEq/L, BUN 16 mEq/L, SCr 1.0 mg/dL, calcium 9.1 mg/dL, magnesium 2.2 mg/dL, albumin 4.6 g/dL, and fasting blood glucose 90 mg/dL. Which one of the following is best to recommend for managing this patient's adrenal disorder?

A. Eplerenone
B. Fludrocortisone
C. Laparoscopic adrenalectomy
D. Metyrapone

14. A 55-year-old man with an adrenal disorder presents to the ED with fatigue, muscle weakness, and inability to walk. His fatigue has worsened over the past week after he initiated a new drug for his adrenal disorder; the patient cannot remember the name of the drug. This morning, he could not walk on awakening. His blood pressure is 112/78 mm Hg, heart rate 56 beats/minute, respiratory rate 19 breaths/minute, and pain score 0/10. In addition to the drug he is taking for an adrenal disorder, he also takes atorvastatin, lisinopril, insulin glargine, and aspirin. Which one of the following drugs is this patient most likely taking for his adrenal disorder?

A. Amiloride
B. Cabergoline
C. Fludrocortisone
D. Pasireotide

15. A 45-year-old woman with a diagnosis of PAI reports for a follow-up visit. Her blood pressure is 138/76 mm Hg, heart rate 78 beats/minute, and weight 67 kg (148 lb; weight 6 months ago, 68 kg [150 lb]). Her laboratory test results today are Na 142 mg/dL, K 4.8 mg/dL, Cl 105 mEq/L, BUN 16 mg/dL, SCr 0.9 mg/dL, calcium 8.2 mg/dL, magnesium 2.1 mEq/L, fasting blood glucose 95 mg/dL, and albumin 2.8 g/dL. She has taken a stable dose of hydrocortisone 20 mg daily and fludrocortisone 75 mcg daily for the past year. Her medical history is significant only for GERD. On questioning, the patient does not appear to have any signs or symptoms of glucocorticoid excess and reports no hypotensive episodes. She does report continued feelings of depressed mood and anxiety and extreme fatigue. Which one of the following is best to recommend for this patient?

A. Initiate dehydroepiandrosterone 25 mg daily.
B. Increase hydrocortisone to 25 mg daily.
C. Decrease fludrocortisone to 50 mcg daily.
D. Change hydrocortisone to prednisolone.

16. A 58-year-old woman with Cushing disease continues to have hypercortisolism despite two TSSs. Her medical history includes depression, dyslipidemia, and osteoporosis. Her blood pressure is 162/82 mm Hg, heart rate 90 beats/minute, respiratory rate 20 breaths/minute, and pain score 0/10. The patient takes rosuvastatin 10 mg orally once daily, bupropion extended release 150 mg orally once daily, alendronate 70 mg orally once weekly, and calcium 500 mg plus vitamin D 400 international units orally once daily. Her laboratory test results today are Na 145 mEq/L, K 3.6 mEq/L, Cl 98 mEq/L, BUN 13 mEq/L, SCr 1.1 mg/dL, calcium 8.4 mg/dL, magnesium 2.1 mg/dL, albumin 4.7 g/dL, and fasting blood glucose 88 mg/dL. Which one of the following is best to recommend for this patient?

A. Etomidate
B. Mifepristone
C. Mitotane
D. Pasireotide

17. A 37-year-old woman reports an increase in urinary frequency and thirst over the past few months. In addition, her coworkers have noted that she is more irritable, and she feels she is "not herself." The patient is concerned about purplish streaks on her chest and abdomen, especially because she will be traveling on a cruise. Her blood pressure is 150/88 mm Hg and heart rate is 84 beats/minute. Her current drugs include levonorgestrel 0.15 mg/ethinyl estradiol 0.03 mg orally once daily and a multivitamin orally once daily. Which one of the following is the best initial test to assess for an adrenal disorder in this patient?

A. 1-mg overnight DST
B. Oral sodium loading test
C. Plasma ACTH concentration
D. Salivary cortisol concentration

18. In a study of pasireotide, investigators were seeking to determine whether patients receiving the drug developed cholelithiasis as a result of treatment. This finding

was documented by assessing the presence or absence of gallstones on an ultrasound examination of the gallbladder. Which one of the following best represents the type of data collected from this study?

A. Interval
B. Nominal
C. Ordinal
D. Ratio

19. Pharmacotherapy is being considered for a 47-year-old man with newly diagnosed Cushing syndrome. He is not a candidate for surgery to correct hypercortisolism because of concerns for bleeding. His blood pressure is 156/90 mm Hg and heart rate is 62 beats/minute. His medical history is significant for hypertension and dyslipidemia, which are managed with lisinopril 10 mg orally once daily, verapamil sustained release 180 mg orally once daily, and rosuvastatin 10 mg orally once daily. Which one of the following is best to recommend for this patient?

A. Cabergoline
B. Ketoconazole
C. Metyrapone
D. Mifepristone

20. A 38-year-old man presents to his primary care provider for a routine physical examination and laboratory tests after feeling more tired than usual over the past several months and experiencing an unintentional 4.5-kg (10 lb) weight loss. His blood pressure is 88/58 mm Hg and heart rate is 64 beats/minute. On physical examination, the patient has dry mucous membranes and reduced skin turgor, as well as reduced muscle strength and areas of hyperpigmentation on the palms of his hands and elbows. The physician suspects adrenal insufficiency. Follow-up laboratory tests show a low serum cortisol, increased ACTH, decreased serum aldosterone, and decreased PRA. Which one of the following is most indicative of PAI versus secondary adrenal insufficiency in this patient?

A. Decreased serum cortisol
B. Increased fatigue
C. Reduced muscle strength
D. Decreased serum aldosterone

Learner Chapter Evaluation: Adrenal Insufficiency, Cushing Syndrome, and Hyperaldosteronism.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Using knowledge of the etiology and pathophysiology of adrenal disorders, classify the type of disorder (e.g., adrenal insufficiency, Cushing syndrome, hyperaldosteronism) for a given patient.
13. Recommend diagnostic testing for a patient with an adrenal disorder.
14. Develop and/or modify a treatment plan including pharmacologic and nonpharmacologic therapies for a patient with an adrenal disorder.
15. Evaluate adverse effects and monitoring values associated with treatments for adrenal disorders.
16. Devise a counseling plan considering both short- and long-term effects of treatment for a given patient with an adrenal disorder.
17. Please provide any specific comments relating to any perceptions of bias, promotion, or advertisement of commercial products.
18. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Hypothyroidism

By Melanie N. Michael, Pharm.D., BCPS

Reviewed by Elizabeth W. Blake, Pharm.D., BCPS; and Maria J. Longo, Pharm.D., BCPS

LEARNING OBJECTIVES

1. Demonstrate an understanding of the physiology of the thyroid gland and etiology of hypothyroidism and subclinical hypothyroidism.
2. Analyze a patient profile to identify potential drug-induced causes of hypothyroidism.
3. Develop and/or modify a treatment plan, including monitoring and patient counseling, for a patient with hypothyroidism or subclinical hypothyroidism.
4. Evaluate complications associated with inadequate treatment and over-supplementation of thyroid hormones.
5. Distinguish clinical presentation and/or pharmacotherapy requirements in special populations, including pediatric patients, pregnant women, older adults, and hospitalized patients.

ABBREVIATIONS IN THIS CHAPTER

FT4	Free thyroxine
LT4	l-Thyroxine, levothyroxine
TBG	Thyroxine-binding globulin
TPOAb	Antithyroid peroxidase antibodies
TSH	Thyroid-stimulating hormone
T4	Thyroxine
T3	Triiodothyronine

Table of other common abbreviations.

INTRODUCTION

After hyperglycemia, hypothyroidism is one of the most common endocrine disorders treated by health care providers. Hypothyroidism results when the thyroid gland lacks sufficient thyroid hormone to satisfy the body's metabolic needs. It is mainly diagnosed with laboratory data and/or clinical signs and symptoms. Overt hypothyroidism has an increased thyroid-stimulating hormone (TSH), also known as thyrotropin, and a decreased free thyroxine (FT4) concentration. In subclinical hypothyroidism, the FT4 concentration is normal, despite an increased TSH. Subclinical hypothyroidism is usually further classified according to a TSH threshold above or below 10 mIU/L (LeFevre 2015).

Epidemiology and Impact

Although the true incidence of hypothyroidism is unknown, the prevalence is estimated to be 4.6% (0.3% overt, 4.3% subclinical) among U.S. individuals 12 years and older. The prevalence increases with age and is higher in females (Boucai 2011). A higher prevalence also occurs in whites, Hispanics, and other ethnicities compared with blacks (Golden 2009; Aoki 2007).

Clinical Guidelines

Various clinical guidelines and recommendation statements provide a framework for the treatment of hypothyroidism in adult patients. The more widely accepted guidelines involve the American Association of Clinical Endocrinologists (AACE) and the American Thyroid Association (ATA) (Jonklaas 2014; Garber 2012). Other guidelines further investigate the treatment of hypothyroidism in pregnant and postpartum women (De Groot 2012; Stagnaro-Green 2011).

Table 2-1. Thyroid Function Test Typical Ranges

Laboratory Test	Typical Range
Thyroid-stimulating hormone (TSH)	0.45–4.12 mIU/L[a]
Total thyroxine (T4)	5.5–12.5 mcg/dL (57–148 nmol/L)
Free thyroxine (FT4)	0.9–2.3 ng/dL (10–26 pmol/L)
Total triiodothyronine (T3)	80–200 ng/dL (1.2–3 nmol/L)
Free triiodothyronine (FT3)	260–480 pg/dL (4–7.4 pmol/L)

[a]In pregnant women, the TSH generalized ranges are trimester-specific: 0.1–2.5 mIU/L for first trimester, 0.2–3 mIU/L for second trimester, and 0.3–3 for third trimester.

Information from: Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism. Thyroid 2014;24:1670-750; Vivian EM, Blackorbay B. Endocrine disorders. In: Lee M, ed. Basic Skills In Interpreting Laboratory Data, 5th ed. Washington, DC: American Society of Health-System Pharmacists, 2013:283-330.

PHYSIOLOGY OF THYROID GLAND

Anatomy of the Thyroid Gland

The thyroid is a butterfly-shaped organ, composed of two lobes in the anterior neck below the laryngeal cartilages. Size and volume vary with age and sex (Chaudhary 2013). Microscopically, the gland consists of follicles, follicular cells, and parafollicular cells, which contribute to iodine absorption and hormone production. This organ is responsible for several physiologic functions that relate to development, growth, and metabolism.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge about the pathophysiology of hypothyroidism
- Diagnostic criteria for hypothyroidism and subclinical hypothyroidism
- Drug knowledge of pharmacologic agents used in treatment of hypothyroidism (mainly levothyroxine)

Table of common laboratory reference values

ADDITIONAL READINGS

The following free resources are available for additional background information on this topic:

- American Association of Clinical Endocrinologists, American Thyroid Association. Clinical Practice Guidelines for Hypothyroidism in Adults. 2012.
- American Thyroid Association Task Force. Guidelines for the Treatment of Hypothyroidism and Other Causes of Thyrotoxicosis. 2016.

Thyroid Hormone and Production Regulation

Two thyroid hormones are produced by the thyroid gland: thyroxine (T4) and triiodothyronine (T3). These hormones are synthesized and stored in the thyroid gland within the protein thyroglobulin. Iodine consumption is essential for the production of thyroid hormones and must be obtained exogenously. Seaweed, seafood, and dairy products are good food sources of iodine. Several countries have salt iodization programs that began in an international public health initiative to minimize iodine deficiency and subsequent hypothyroidism. In the United States, iodine has been added to salt since the early 1900s, and iodized salt contains 45 mcg of iodine per gram of salt. According to the WHO, the recommended dietary allowance for nonpregnant adults is 150 mcg of iodine daily. This amount is increased up to 250 mcg for pregnant or lactating women. Overall, iodine intake in the United States is sufficient, and supplementation is usually not required. However, pregnant women who do not consume dairy products and who minimize their intake of iodized salt may be at an increased risk of iodine deficiency and subsequent hypothyroidism (Leung 2014; NIH 2011).

Most thyroid hormones are bound to proteins in the serum. Thus, only the FT4 and T3 concentrations determine biological activity (Table 2-1). Although T4 is exclusively produced by the thyroid gland, T3 is produced by the thyroid and is also derived from other tissues. Although T4 is produced in greater amounts, T3 is considered the more biologically active form. Eighty percent of T3 is produced from the peripheral conversion of T4 by deiodination. Thus, changes in the deiodinase activity and protein binding influence the activity of thyroid hormones. Reverse T3, produced from the peripheral deiodination of T4, plays a role in critical illness. Almost all of T4 is bound to T4-binding globulins (TBGs), T4-binding prealbumin, and albumin. Comparatively, T3 is most tightly bound to albumin and less to the other serum proteins. Patients who have pharmacogenomic polymorphisms in the deiodinases

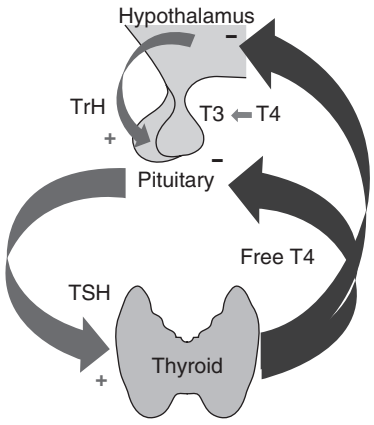

Figure 2-1. Thyroid function. The hypothalamus releases thyrotropin-releasing hormone (TrH), which travels by a venous plexus to the anterior lobe of the pituitary gland and stimulates the release of thyroid-stimulating hormone (TSH). TSH then induces the production of thyroxine (T4) by the thyroid. In response to the free T4 (FT4) concentrations, which influence the amount of triiodothyronine (T3) produced in each site, both the hypothalamus and the pituitary alter production of TrH and TSH, respectively. Elevated FT4 inhibits production, whereas low FT4 stimulates production.

Reprinted with permission from: Faix JD, Thienpont LM. Thyroid-Stimulating Hormone: Why Efforts to Harmonize Testing Are Critical to Patient Care. American Association of Clinical Chemistry, 2013.

or serum proteins may have alterations in the circulating concentrations of these various thyroid hormones. Estrogens are associated with increased TBGs and T4, whereas androgens are associated with decreased TBGs and T4.

Thyroid hormone production is regulated in two ways. The main mechanism is by a negative feedback system that involves the hypothalamus, anterior pituitary, and thyroid gland (Figure 2-1). Low concentrations of thyroid hormones stimulate the release of thyrotropin-releasing hormone (TRH), which results in the release of TSH from the anterior pituitary and a subsequent increased secretion of thyroid hormones. High concentrations of thyroid hormones would inhibit the release of TRH and the resulting cascade. There is a log-linear relationship between the hormones, such that small changes in FT4/FT3 result in large changes in TSH. The secondary mechanism for thyroid hormone regulation is by the extrathyroidal conversion of T4 to T3.

Etiology

The etiologies for hypothyroidism are vast and differ according to the sex, age, genetics, and overall health of the patient. Many medications also contribute to the development of hypothyroidism.

Primary Hypothyroidism

Primary hypothyroidism accounts for most hypothyroidism cases. A low FT4 with an appropriately elevated TSH is representative of primary hypothyroidism. In iodine-sufficient locations, such as the United States, the most common cause of primary hypothyroidism is chronic autoimmune thyroiditis, also known as Hashimoto thyroiditis. Autoimmune thyroid disease frequency increases with age. This disorder is also more common in women and families with other autoimmune disorders. Autoimmune thyroid disease is diagnosed with the presence of elevated antithyroid antibody titers (Almandoz 2012). These include antithyroglobulin antibodies, antithyroid peroxidase antibodies (TPOAb), and TSH receptor antibodies. Individuals may have elevated titers of these antibodies and still be in a euthyroid state. However, of these autoantibody markers, elevated TPOAb titers are most predictive of progression to overt hypothyroidism (Jonklaas 2014; Garber 2012).

Radiation and surgical removal of the thyroid gland can also result in hypothyroidism. Whereas radiation and partial removal of the thyroid gland may allow hormone secretion to remain sufficient for daily functioning, removal of the entire thyroid gland always results in hypothyroidism, necessitating lifelong supplementation. Congenital hypothyroidism is present at birth and requires early and adequate treatment to prevent physical and neurocognitive developmental delays. Hypothyroidism in pregnancy is usually the result of Hashimoto disease. But postpartum thyroiditis results in a short period (less than 2 months) of hyperthyroidism, which is subsequently followed by hypothyroidism. Postpartum thyroiditis may go undiagnosed because initial symptoms are often attributed to postpartum depression (Garber 2012).

Central Hypothyroidism

Central hypothyroidism occurs when there is inadequate stimulation of a normal thyroid gland. This is because of either decreased hypothalamic responsiveness to low circulating concentrations of thyroid hormones or anterior pituitary failure to appropriately release TSH. Most central hypothyroidism cases are the result of pituitary tumors. With central hypothyroidism, TSH concentrations are not appropriately elevated in the presence of a low FT4. This must be considered when establishing the treatment goals in central hypothyroidism.

Drug-Induced Hypothyroidism

Several medications have hypothyroidism as a well-documented adverse effect (Box 2-1). One of the most notable agents implicated is amiodarone. This drug is an antiarrhythmic used for the treatment of atrial and ventricular arrhythmias and may also be indicated for rhythm control in the setting of heart failure with reduced ejection fraction. The drug can also be used for rate control when preferred agents such as β-blockers and non-dihydropyridine calcium channel blockers are contraindicated. Of note, an adverse effect of amiodarone is that it may cause either hypothyroidism or hyperthyroidism.

Box 2-1. Mechanisms for Drug-Induced Thyroid Function Abnormalities

Effects on thyroid gland

Iodine uptake
- Amiodarone
- Iodine

Hormone production
- Amiodarone
- Iodine
- Thionamides

Hormone secretion
- Amiodarone
- Iodine
- Lithium

Thyroiditis
- Amiodarone
- Lithium
- Interferon alfa
- Tyrosine kinase inhibitors

Effects on thyroid hormone metabolism

Absorption
- Calcium, iron, and aluminum-containing products (i.e., antacids)
- Bile acid binding resins
- Sucralfate
- Orlistat
- Phosphate binders

Clearance
- Antiepileptics (phenytoin, phenobarbital, carbamazepine)
- Rifampin
- Tyrosine kinase inhibitors

Peripheral metabolism
- Glucocorticoids
- Amiodarone
- β-Blockers

Information from: Garber JR, Cobin RH, Gharib H. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association.

Amiodarone contains iodine in its chemical structure, which is mainly responsible for its effects on the thyroid. Hypothyroidism is more prevalent in iodine-sufficient areas, whereas hyperthyroidism is more common in iodine-deficient areas. The reason that hypothyroidism is more common in iodine-sufficient regions can be explained by the Wolff-Chaikoff effect, whereby the body does not acutely secrete more thyroid hormones in the presence of excess iodine made available by metabolism of amiodarone. The effect lasts several days; then, the body usually "escapes" this inhibition and resumes usual synthesis of thyroid hormones. This escape phenomenon occurs because of decreased expression of the sodium-iodide-symporter, which is responsible for the transport of iodine from the circulation into the thyroid gland. The high iodine content of amiodarone inhibits the activity of one of the deiodinases, resulting in decreased T4 to T3 conversion and a subsequent increase in TSH secretion. Failure to escape the Wolff-Chaikoff effect ultimately leads to iodine-induced hypothyroidism. Risk factors include female sex, higher amiodarone doses, and presence of TPOAb (Leung 2014; Padmanabhan 2010; Eskes 2009).

Lithium is also known to cause both hypothyroidism and hyperthyroidism. Lithium is used to treat bipolar disorder and is highly concentrated in the thyroid gland. With respect to lithium-induced hypothyroidism, lithium inhibits thyroid hormone secretion and release, thus signaling an increase in TSH and possible goiter development. This inhibition of thyroid hormone secretion and release is because of tubulin polymerization alterations together with TSH effects on cyclic adenosine monophosphate. Lithium also enhances thyroid autoimmunity, if already present before treatment. Low iodide uptake results from lithium-induced iodide retention and competition for the iodide transport within the thyroid gland. Risk factors for developing lithium-induced hypothyroidism include female sex and therapy initiation at a later age (Kibirige 2013; Lazarus 2009).

Interferon alfa, commonly used in the treatment of hepatitis C, causes hypothyroidism through an induction of thyroiditis. As mentioned with amiodarone and lithium, this agent can also cause hyperthyroidism. Interferon-induced thyroid disorders may present as immune or non-immune thyroiditis, but Hashimoto thyroiditis is the most common manifestation of interferon-induced thyroiditis. The presence of pre-interferon treatment TPOAb is a risk factor for developing autoimmune thyroid disease. Although interferon alfa has some direct effects on the thyroid gland, patients with hepatitis C also have a correlation with an increased risk in thyroid abnormalities (Tomer 2009).

Newer drugs that have reported hypothyroidism as a drug-induced effect include the tyrosine kinase inhibitors of the vascular endothelial growth factor pathway. Tyrosine kinase inhibitors are used to treat a variety of malignancies. Sunitinib and sorafenib have the most evidence; however, hypothyroidism is presumed to be a class effect. These drugs induce hypothyroidism through various mechanisms, including (1) enhancement of capillary regression in thyroid vascular system and (2) direct inhibition of thyroid cell growth. Clinicians should be aware of the overlap in signs and symptoms of drug therapy and hypothyroidism. Hypothyroidism, together with other adverse effects with tyrosine kinase inhibitors, is called a mechanism-based toxicity. These toxicities are theorized to provide predictive value regarding positive response to therapy and mortality benefit (Dienstmann 2011).

Overtreatment of hyperthyroidism can lead to a hypothyroid state. Thus, it is important to monitor both the laboratory values and the signs and symptoms of patients receiving therapy for hyperthyroidism (i.e., thionamides) to ensure that thyroid oversuppression does not occur.

Diagnosis and Clinical Presentation

Different organizations have varying screening recommendations for nonpregnant adults. Routine screening of all individuals currently is not recommended by any organization. The ATA has more stringent screening recommendations beginning at 35 years of age and every 5 years for women and men. However, AACE and the American College of Physicians recommend screening of older patients, with an emphasis placed on women with suggestive clinical symptoms. The American Academy of Family Physicians has endorsed the U.S. Preventive Services Task Force's updated recommendation that current evidence is insufficient to assess the balance of benefits and harms of screening for thyroid dysfunction in nonpregnant, asymptomatic adults (AAFP 2015). Each organization recognizes the significance of routine screening in pediatric patients and pregnant women.

The ATA/AACE-cosponsored guidelines acknowledge compelling evidence to support population screening in patients with specified risk factors, including individuals with autoimmune disease or a first-degree relative with autoimmune thyroid disease, psychiatric disorders, pernicious anemia, history of neck radiation or thyroid surgery, and patients taking amiodarone or lithium (LeFevre 2015; Rugge 2015; Gaitonde 2012).

The diagnosis of hypothyroidism is mainly laboratory driven. Third-generation TSH assays are the most widely used and are the most sensitive tests for primary hypothyroidism. However, use of TSH for diagnosis is unreliable when the hypothalamic-pituitary-axis is not intact or the thyroid status is not stable. The hallmark laboratory features include an elevated TSH together with a decreased FT4. Reference intervals, which are based on age, vary slightly among different laboratories. However, if the laboratory does not have a defined age-based upper limit, the ATA/AACE consensus statement recommends that a TSH upper limit of 4.12 mIU/L be considered for all nonpregnant adults. In addition to laboratory abnormalities, patients may present with a wide array of signs and symptoms (Box 2-2). These symptoms usually become more evident at higher TSH concentrations. Other clinical manifestations and conditions that may warrant screening for hypothyroidism include lipid abnormalities, hyponatremia, macrocytic anemia, and autoimmune disorders. Older adult patients have slightly increased normal TSH concentrations. Thus, a TSH concentration that would be considered slightly out of range for a younger individual is typically within the normal expected range for an older adult. For patients with central hypothyroidism in which the thyroid is normal but is not properly stimulated, TSH concentrations are unreliable. These concentrations are also not recommended in hospitalized patients who are commonly taking drugs, such as glucocorticoids and dopamine agonists, that lead to TSH suppression (Sehgal 2014). Thyroid-stimulating hormone is an acute-phase reactant; thus, concentrations may be altered and are unreliable during periods of acute illness. Because errors may occur with TSH monitoring, some experts advocate screening with both TSH and FT4 concentrations initially, although this likely results in unnecessary costs. There is also an alternative testing approach called TSH with reflex to FT4. In this scenario, the FT4 is tested only if the TSH is out of range.

Box 2-2. Signs, Symptoms, and Conditions Associated with Hypothyroidism

Well known:

- Fatigue
- Weight gain (or difficulty losing weight)
- Cold insensitivity
- Muscle cramps
- Constipation
- Dry skin

Less well known:

- Carpal tunnel syndrome
- Sleep apnea
- Pituitary hyperplasia (with or without hyperprolactinemia and galactorrhea)

Information from: Garber JR, Cobin RH, Gharib H. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association.

Treatment

The standard treatment for hypothyroidism is administration of L-thyroxine, levothyroxine (LT4) preparations. Several brand and generic products exist in oral, color-coded strengths of 25–300 mcg. The 50-mcg tablet is white and is recommended in patients who have allergies to the color additives used in the other tablets. In general, there is no preference for branded products to generic as long as the same generic can be maintained. A parenteral formulation of levothyroxine is available for patients who cannot tolerate anything orally for an extended period. The ATA guidelines recommend an intravenous dose that is 75% of the oral dose, according to the premise that under optimal fasting conditions, the absorption of oral levothyroxine is 70%–80%. However, the intravenous-to-oral dose conversion most often used clinically is 1:2; thus, the intravenous dose would be one-half of the established oral dose. This practice likely reflects the lack of optimal absorption that commonly occurs among patients taking levothyroxine. The daily dose depends on age, sex, and lean body mass, which is the best predictor of daily dose. The usual starting daily weight-based dose is 1.6 mcg/kg in young and healthy patients, or alternatively 100 mcg. Older adult patients and patients with cardiovascular disease are typically initiated at 25–50 and 12.5–25 mcg, respectively (Table 2-2). Doses, which are on the lower end of the dosing range, are initiated because full-repletion doses in

Table 2-2. Levothyroxine Dosing

Population	Recommended Initial Daily Dose
Adults (young)[a,b]	1.6 mcg/kg
Older adults[a]	25–50 mcg
Pediatric patients:	
Newborns	10–15 mcg/kg
1–3 yr	4–6 mcg/kg
3–10 yr	3–5 mcg/kg
10–16 yr	2–4 mcg/kg

[a]Patients with known cardiovascular disease should be initiated at 12.5–25 mcg.

[b]Pregnant patients may require a 30%–50% increase during pregnancy.

Information from: Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism. Thyroid 2014;24:1670-750.

these patients can worsen myocardial ischemia by increasing myocardial oxygen consumption. Because older adult patients have higher baseline TSH concentrations, treatment goals should reflect this, and acceptance of higher TSH concentrations is likely appropriate. Dose adjustments are typically made in increments of 12.5–25 mcg/day at 4- to 6-week intervals. In primary hypothyroidism, normalization of FT4 concentrations with a consistently elevated TSH usually hints at nonadherence. Evidence supports once- or twice-weekly dosing of the full-replacement levothyroxine dose (i.e., 7 times the daily dose) if there is a problem with adherence in older adult patients (Jonklaas 2014; Garber 2012).

Other therapies available for the treatment of hypothyroidism include liothyronine (LT3) and combination T4/T3 desiccated products. Although available on the market, these agents are not routinely recommended by ATA or AACE because supplementation with LT4 is usually adequate for restoring normal thyroid function. However, the 2014 ATA guidelines acknowledge that not all patients may achieve a euthyroid state with levothyroxine alone. The guidelines also note that despite a lack of evidence supporting the use of combined levothyroxine and liothyronine or combined desiccated products over levothyroxine monotherapy, some patients have a clinical response with these other regimens. Liothyronine may be used when a patient needs to discontinue levothyroxine, such as for a diagnostic procedure, which would be affected by the thyroid hormones. Liothyronine has a shorter half-life (48 hours) than levothyroxine (1 week). Thus, it can be discontinued for a shorter period before the procedure (McAninch 2016; Jonklaas 2014).

The desiccated products are natural substances derived from porcine sources and there are concerns about product consistency as well as potential for allergic reactions. The desiccated product contains 38 and 9 mcg of T4 and T3, respectively, per 1 grain (60–65 mg). However, information from trials and clinical evidence suggests that the ratio is actually larger. Thus, the United States Pharmacopeia uses

Patient Care Scenario

A 62-year-old woman (current weight 100 kg [220 lb]; weight 6 months ago 82 kg [180 lb]) who has no significant medical history is seen in the family medicine clinic with complaints of fatigue, constipation, dry skin, and being cold most of the time. Her current medications include amlodipine and a once-daily women's vitamin. She states that she does not like to take medications and admits nonadherence to her current medications. Significant laboratory data include TSH 15 mIU/L, FT4 0.5 ng/dL, TC 250 mg/dL, LDL 160 mg/dL, and Hgb 12.4 mg/dL. The cholesterol concentrations were elevated, and the Hgb concentration was lower than during her previous visit. What is the appropriate treatment for this patient?

ANSWER

The patient presents with clinical signs and symptoms as well as laboratory evidence of hypothyroidism. Given her weight (100 kg [220 lb]), her weight-based daily levothyroxine dose would be 160 mcg. However, levothyroxine is not available in this strength. It is available in both 150- and 175-mcg tablets. Because an alternative strategy to initiating levothyroxine is to initiate it at 100 mcg and titrate it accordingly, it would be reasonable to use the lower 150-mcg dose. Regarding adherence issues, evidence has shown success with the administration of levothyroxine once or twice weekly. Thus, if the patient were taking 150 mcg daily, she could take all 7 tablets once weekly. The weekly dose can also be calculated initially as 1120 mcg weekly (1.6 mcg/kg x 100 kg x 7 days/week = 1120 mcg/week), which could then be administered as ten 112-mcg tablets once weekly or five 112-mcg tablets twice weekly. A TSH concentration should be measured 4–6 weeks after initiating therapy to assess the need for dose modifications.

1. Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Endocr Pract 2012;18:988-1028.

2. Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism. Thyroid 2014;24:1670-751.

a conversion of 1 mg desiccated product = 1.667 mcg of LT4 product and suggests 1 grain of desiccated thyroid is equivalent to 100 mcg of T4. In two recent studies, patients reported higher levels of satisfaction with their hypothyroidism treatment when they were changed from levothyroxine to a desiccated thyroid product (Pepper 2014; Hoang 2013).

Selenium is an essential mineral required for the conversion of T4 to T3. Thus, it is no surprise that it has been studied in hypothyroidism. It has shown some benefits in patients with Hashimoto thyroiditis who were already being treated with levothyroxine. Selenium decreased anti-thyroid peroxidase antibodies (TPOAb) and improved mood but did not demonstrate any significant ultrasonographic changes (Toulis 2010).

Complications

If left untreated, hypothyroidism can cause serious health concerns. Constant stimulation of the thyroid gland can result in a goiter. Peripheral neuropathy and myopathy can occur if hypothyroidism is not diagnosed and properly treated. Myxedema in older adults is a rare but life-threatening condition associated with long-term untreated hypothyroidism. The hallmark features include mental status changes followed by unconsciousness and hypothermia. Hyponatremia, hypercapnia, and bradycardia are associated clinical findings often seen with myxedema. The condition is more likely to occur in older adult women with a history of primary hypothyroidism. Initially, patients should receive a 200- to 400-mcg intravenous loading dose of levothyroxine. However, older adult patients and those with cardiovascular disease may require reduced loading doses. Then, patients can be initiated on 75% of the usual full replacement daily dose of 1.6 mcg/kg as long as the drug is being given intravenously. Intravenous liothyronine may be given in addition to levothyroxine because T4 conversion to T3 may be reduced in patients with myxedema. High liothyronine concentrations are associated with increased mortality and should be avoided. Thus, a loading dose of 5–20 mcg can be given, followed by a maintenance dose of 2.5–10 mcg every 8 hours. The optimal duration for this levothyroxine and liothyronine combination therapy has not been established. Monitoring T3 and T4 serum concentrations 24–48 hours after the loading dose could provide evidence about the response to the loading dose. Although the TSH concentrations would not be expected to reach steady state for a while, serial measurements of TSH, T4, and T3 could provide evidence of efficacy and ensure that high T3 concentrations are avoided. Empiric glucocorticoids should be administered in appropriate stress doses before intravenous levothyroxine. Patients with myxedema should be monitored closely in an ICU until clinical signs and symptoms improve. Patients with myxedema coma have a high mortality rate, even with appropriate treatment (Jonklaas 2014; Gaitonde 2012).

Cardiovascular changes in hypothyroidism include a decrease in heart rate and contractility with an increase in peripheral vascular resistance. Other surrogate markers of cardiovascular disease that are altered in hypothyroidism include elevations in atherogenic lipid concentrations, increase in carotid intima thickness, and diastolic blood pressure elevation. Women of childbearing age may have infertility because of impaired ovulation, and infants born to women with untreated hypothyroidism have a higher incidence of birth defects (Garber 2012).

Subclinical Hypothyroidism

Subclinical hypothyroidism is a laboratory diagnosis with elevated TSH and normal FT4. Clinical symptoms may or may not accompany these laboratory changes. The etiology of subclinical hypothyroidism is similar to that of primary hypothyroidism. One of the biggest controversies surrounding subclinical hypothyroidism is whether to treat. It is widely accepted that treatment should be initiated in any adult patient with LT4 when the TSH is greater than 10 mIU/L. These patients usually do not require full replacement doses and can usually normalize TSH with a 25–75 mcg daily dose. However, when the TSH is 4.5–10 mIU/L, there is disagreement on the benefits-risks of treatment. Recommendations vary regarding treatment in children and in pregnant women with subclinical hypothyroidism, even with TSH concentrations greater than 10 mIU/L. Specific trimester cutoffs have been designated for when to initiate treatment in pregnant women (Pearce 2013; Garber 2012). Risk factors should be considered when deciding whether to treat a patient with mild subclinical hypothyroidism (Box 2-3).

Subclinical hypothyroidism has been associated with an increased risk of coronary heart disease and heart failure, particularly in patients with the highest TSH concentrations. The presence of TPOAb does not seem to worsen this risk. Several studies have shown beneficial responses in atherogenic lipids, impaired endothelin function, and carotid intima thickness with treatment even at mildly elevated TSH concentrations. An ongoing randomized, placebo-controlled trial, Thyroid Hormone Replacement for Untreated Older Adults with Subclinical Hypothyroidism (TRUST), is currently under

Box 2-3. Factors to Consider for Initiating Levothyroxine in Mild Subclinical Hypothyroidism

- Thyroid-stimulating hormone concentration
- Goiter presence
- Age
- Pregnancy (or intended pregnancy)
- Presence of antithyroid antibodies
- Cardiovascular disease

Information from: Zeeshan J, Sathyapalan T. Levothyroxine treatment of mild subclinical hypothyroidism: a review of potential risks and benefits. Ther Adv Endocrinol Metab 2016;7:12-23.

way in the UK and Switzerland. The trial will assess the impact of T4 replacement in 540 older adults who have persisting subclinical hypothyroidism. Outcomes include health-related quality of life, executive cognitive function, muscle strength, and cardiovascular outcomes. The follow-up period will be a minimum of 1 year, and the study's expected completion date is February 2017 (Gencer 2016; Collet 2014; Rodondi 2010).

MONITORING

The TSH and FT4 concentrations should be monitored 4–6 weeks after initiation of therapy, dose changes, or any other events that may be expected to alter thyroid functioning or therapy efficacy. With central hypothyroidism, clinicians must rely on FT4 concentrations and symptom improvement because an inadequate TSH response occurs, despite adequate supplementation. After a euthyroid state is achieved, thyroid function tests are recommended semiannually to annually in nonpregnant adult patients. Children, especially those with severe hypothyroidism, and pregnant patients require more frequent monitoring. Various intervals are recommended for this increase in frequency, from 2 to 4 weeks after initiating therapy in infants and children with severe hypothyroidism, followed by every 1- to 2-month testing during the first year of life. For a child with severe congenital hypothyroidism, the goal is to normalize T4 concentrations within 2–4 weeks. During the first half of pregnancy, every-4-week monitoring is recommended (Jonklaas 2014; De Groot 2012).

PATIENT COUNSELING

In general, the products should be taken on an empty stomach with water only about an hour before breakfast because this provides better absorption. Although fasting may optimize the absorption of levothyroxine, it may also result in decreased adherence because of inconvenience. If fasting is not feasible, dosing LT4 3 hours after dinner also maintains steady thyroid hormone concentrations. If patients initially take LT4 with food and then start the recommended method of administration, thyroid concentrations should be rechecked to assess whether any dose changes are warranted on the basis of changes in absorption. Bile acid–binding resins, sucralfate, and cationic salts (including aluminum, iron, and calcium) can impair the absorption of levothyroxine, and a 4-hour separation of doses has traditionally been recommended. However, an optimal separation period has not been established. All prescription thyroid hormone replacement products carry a boxed warning related to their ineffectiveness and potential toxicity when used for weight reduction in a patient in a euthyroid state.

SPECIAL POPULATIONS

The information discussed to this point has mainly focused on hypothyroidism and subclinical hypothyroidism in the general nonpregnant adult population. Other populations may require more aggressive monitoring and treatment.

Infants and Children

Congenital hypothyroidism affects 1 in 2000–4000 newborns and is one of the most common treatable causes of physical and neurocognitive developmental delays. Screening for hypothyroidism occurs within the first few days of life (Gruters 2012). The recommended treatment is LT4 tablets, which should be crushed and placed in breast milk or non-soy formula. The medication should also be separated from iron, calcium, and antacids because of the decreased absorption of LT4 with concomitant administration of these agents. Dosing and monitoring recommendations are age-dependent (see Table 2-2).

Hashimoto thyroiditis is one of the more common autoimmune endocrine disorders in the pediatric population and is usually diagnosed according to the presence of antithyroid antibodies and ultrasonographic pattern. The condition is more prevalent among children who have other autoimmune and chromosomal disorders, including type 1 diabetes, celiac disease, and Down, Klinefelter, and Turner syndromes. The most common manifestation of hypothyroidism in children is decreased growth velocity that occurs slowly. Because of this gradual onset, it may be present for a long time before being recognized (de Vries 2009). A common physical finding is a goiter. Altered performance in school is a common presentation. Pediatric patients should receive an early diagnosis to prevent any developmental delays. Children with obesity may have ultrasonographic patterns similar to those with Hashimoto thyroiditis without being affected. Obesity does cause an increase in TSH concentrations, but the increase usually remains in the subclinical range. Weight loss is the recommended treatment for these patients because TSH concentrations usually normalize afterward. Children with overt hypothyroidism should be treated with LT4, but those with subclinical hypothyroidism may not require treatment because evidence does not suggest any physical or cognitive delays in this group. Children with central hypothyroidism should undergo cranial imaging and be evaluated for other pituitary disorders (Radetti 2014).

If treatment with LT4 is required for acquired hypothyroidism, children will require higher weight-based dosing than adults because of increased clearance (see Table 2-2). Alternatively, a dose for children can be calculated using body surface area at any age as around 100 mcg/m^2/day. For monitoring, the recommended target range for TSH is in the lower half of reference range and in the upper half of the reference range for FT4.

Pregnant Women

Several physiologic changes occur during pregnancy that help meet increased metabolic requirements. Notable changes relative to the thyroid include increased gland size, production of

T3 and T4, and TBGs. Thyrotropic activity of human chorionic gonadotropin results in a decreased TSH. These changes may result in hypothyroidism in later trimesters of pregnancy in a female previously in a euthyroid state. Reference ranges for TSH throughout pregnancy are trimester-specific and lower than in the general adult population. The generalized TSH reference ranges for pregnancy are lower than in the general population (see Table 2-1). There are also slight ethnic variations in TSH concentrations during pregnancy. Black and Asian patients tend to have slightly lower concentrations.

Dietary and medication requirements change and must consider both the health of the mother and health of the infant as well as the associated risks and adverse effects. Levothyroxine had a FDA pregnancy category A rating, according to the old labeling requirements. Studies of women taking levothyroxine have not shown an increase in congenital abnormalities. Treatment of hypothyroidism in pregnancy is fairly simple. Most women will require an increase in levothyroxine dose throughout the pregnancy. The dose adjustment will vary, depending on the underlying cause of hypothyroidism, and should be made early or before pregnancy. For women already taking levothyroxine, two extra doses per week can be started after pregnancy is confirmed. Two-thirds of women may need up to a 30%–50% dose increase. Thyroid function should be measured every 4 weeks during the first half of pregnancy when dosing requirements are most likely to change. Another assessment of thyroid function should be done during the third trimester. Most women return to their pre-pregnancy dose after delivery and should have TSH assessed 6 weeks post-delivery. Both under- and over-supplementation can have deleterious effects on both the mother and the fetus. Untreated or improperly treated hypothyroidism during pregnancy can result in impaired cognitive and motor skill development in the child (Pearce 2015; De Groot 2012; Stagnaro-Green 2011).

Treatment of subclinical hypothyroidism in pregnant women is controversial, as in other special populations. Although the effects of not treating women with overt hypothyroidism have been shown, information is much more conflicting regarding the risks of no treatment versus the benefits of levothyroxine treatment. Women who are not treated should be monitored for progression to overt hypothyroidism. This includes having TSH and FT4 monitored at the same frequency mentioned for pregnant women receiving levothyroxine. A recent meta-analysis found an increase in several adverse pregnancy and neonatal outcomes, including placenta abruption, premature rupture of membranes, pregnancy loss, and neonatal death, associated with subclinical hypothyroidism. However, this review stated that the value of levothyroxine therapy in preventing these events remains unclear. Moreover, data from a small prospective cohort study failed to show an increased risk in pregnancy loss or stillborn births. Other pregnancy-related conditions linked to increasing TSH include gestational diabetes and hypertension (Maraka 2016; Plowden 2016; Lazarus 2014).

Older Adult Patients

Metabolic processes are altered as patients grow older. Some noteworthy changes in thyroid function associated with aging are a decrease in thyroid hormone production and metabolism. In patients with several comorbidities, signs and symptoms of hypothyroidism may be overlooked or mistaken for other conditions such as depression and dementia.

Older adult patients usually have lower LT4 requirements when supplementation is warranted. The reasons for this are multifactorial and include a decrease in body mass and metabolic clearance, slowly progressing thyroid dysfunction, decrease in lean body mass, and, potentially, medication interactions. If thyroid hormone replacement is initiated too aggressively in older adult patients with baseline cardiovascular disease or several comorbidities, they may have angina, increased shortness of breath, heart failure, and confusion. If any of these clinical symptoms occur, the dose should be decreased and titrated more slowly. Most experts recommend increasing the daily levothyroxine dose by 12.5–25 mcg every 4–6 weeks until thyroid function tests are normalized (Sehgal 2014; Gesing 2012).

Practice Points

Hypothyroidism is fairly easy to manage, once properly diagnosed. Yet controversy remains regarding the treatment of subclinical hypothyroidism. Special considerations must be made when treating overt hypothyroidism or subclinical hypothyroidism in select patient populations.

- **Hypothyroidism is a laboratory-driven diagnosis with an elevated TSH in the presence of low thyroid hormones.**
- **Hashimoto thyroiditis, an autoimmune disease, is the most common type of primary hypothyroidism and occurs more commonly in females and patients older than 60.**
- **Weight gain, fatigue, constipation, and dry skin are commonly recognized as signs of hypothyroidism, whereas carpal tunnel syndrome, sleep apnea, and pituitary hyperplasia are more likely to be overlooked signs and symptoms.**
- **Medications can affect thyroid functioning by several mechanisms, including alterations in iodine uptake, production and/or secretion of thyroid hormones, and modulating inflammatory mediators.**
- **Levothyroxine is the treatment of choice for hypothyroidism and is safe in all populations when dosed appropriately.**
- **Physiologic changes in pregnancy include increases in thyroid gland size, production of thyroid hormones, and iodine requirements.**
- **The decision to treat or not to treat subclinical hypothyroidism should consider factors such as presence and size of goiter, age, pregnancy, and presence of preexisting cardiovascular disease.**
- **Data are conflicting regarding the risks in both maternal and fetal outcomes associated with subclinical hypothyroidism.**

Hospitalized Patients

Hospitalized patients provide yet another unique situation in the assessment and treatment of hypothyroidism. Physiologic changes occur during an acute illness that may affect the thyroid system. Therefore, routine thyroid monitoring is not recommended during acute illness. Critically ill patients have a decreased conversion of T4 to T3 secondary to cytokine-induced inhibition of deiodinases, which is responsible for the conversion. These patients tend to have high reverse T3 concentrations, except when renal failure is present. This clinical picture is often called sick euthyroid syndrome or non-thyroid illness syndrome and is the body's mechanism for reducing catabolism in acute illness. The presence of reverse T3 concentrations can help distinguish central hypothyroidism from sick euthyroid syndrome. Medications used during acute illnesses can also be major contributors to alterations in thyroid function tests. For patients who are not critically ill, oral levothyroxine is recommended. Another enteral route may be used if the oral route is not feasible. Intravenous levothyroxine may be used if concerns for enteral absorption are expected to remain for an extended period (Jonklaas 2014; Sehgal 2014).

CONCLUSION

Hypothyroidism is mainly a laboratory-based condition that is easily treated with levothyroxine. Assessment and treatment of subclinical hypothyroidism is more controversial. Many factors contribute to the diagnosis of hypothyroidism, including age, sex, genetic predispositions, and concomitant medications. Hypothyroidism and subclinical hypothyroidism can occur in special populations, including pediatric patients, pregnant women, older adults, and hospitalized patients. Treatment must be carefully implemented, and clinicians must be aware of the risks associated with improper treatment. Whether to treat subclinical hypothyroidism remains an ongoing clinical controversy.

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Self-Assessment Questions

Questions 21 and 22 pertain to the following case.

R.J. is a 72-year-old man (weight 75 kg) who received a diagnosis of hypothyroidism a few years ago. At the time, he was taking no medications and had no significant medical history. R.J. decided he would only take a natural product, so he was initiated on ½ grain of T4/T3 desiccated thyroid product.

21. Which one of the following is most significant to R.J.'s thyroid function?

    A. Increased concentrations of thyroid-binding globulins
    B. Decreased lean body mass
    C. Increased thyroid-stimulating hormone (TSH) concentrations
    D. Decreased total body mass

22. Upon the recommendation of a clinical pharmacist, the physician has decided to change R.J. to a T4 product. Which one of the following doses is best to recommend for R.J.?

    A. 25 mcg
    B. 50 mcg
    C. 75 mcg
    D. 100 mcg

23. A patient with hypertension, atrial fibrillation, hepatitis C, and renal carcinoma is being treated with lisinopril, amiodarone, interferon alfa, ribavirin, sorafenib, and dexamethasone. Which one of the following drugs is most likely to interfere with this patient's production and secretion of thyroid hormones, as well as alter iodine uptake?

    A. Sorafenib
    B. Amiodarone
    C. Dexamethasone
    D. Interferon alfa

Questions 24–26 pertain to the following case.

K.M. is a 33-year-old pregnant woman who is just entering her second trimester. She has complaints of general fatigue, hair loss, and extremely dry skin. K.M. was hesitant to discuss these concerns with her obstetrician because she assumed that these signs and symptoms were related to hormonal changes.

24. Which one of the following is most important to consider regarding hypothyroidism screening in K.M.?

    A. According to U.S. Preventive Services Task Force, she should not be screened.
    B. According to ATA, she should be screened because of her age.
    C. According to American Academy of Family Physicians, she should not be screened.
    D. According to AACE, she should be screened because of her pregnancy status.

25. Which one of the following statements is most important for the obstetrician to consider about hormone replacement therapy for K.M.?

    A. Her maximal thyroid replacement dose was likely required during the first trimester.
    B. Her postpartum thyroid replacement dose will likely be lower than during pregnancy.
    C. Her thyroid replacement dose does not require titration during her pregnancy.
    D. Her thyroid replacement needs are not expected to differ from those of a nonpregnant adult.

26. Which one of the following best describes the risk if K.M. does not receive proper T4 supplementation during pregnancy?

    A. Increased risk of miscarriage
    B. Increased risk of diabetes mellitus
    C. Decreased childhood motor skills development
    D. Decreased fetal neurologic development

Questions 27 and 28 pertain to the following case.

T.Y. is a 36-year-old African American woman with type 2 diabetes. She is seen in the family medicine clinic for an annual wellness physical examination. T.Y. has had a positive antithyroid peroxidase antibodies (TPOAb) titer in the past but remains asymptomatic.

27. Which one of the following is the strongest predictor for developing hypothyroidism in T.Y.?

    A. Sex
    B. Age
    C. Type 2 diabetes
    D. TPOAb

28. Considering her age, which one of the following organizations would most strongly recommend screening in T.Y.?

    A. U.S. Preventive Services Task Force
    B. American Academy of Family Physicians
    C. ATA
    D. AACE

29. A 55-year-old man with obesity recently received a diagnosis of subclinical hypothyroidism. His medical history includes hypertension, type 2 diabetes, and elevated TC and LDL. Which one of the following values is most likely to improve with levothyroxine supplementation in this patient?

A. Weight
B. LDL
C. A1C
D. Systolic blood pressure

30. A patient with negligible thyroid function currently takes 150 mcg of levothyroxine daily. She was recently given a diagnosis of allergies to several color additives. Which one of the following strategies is best to implement to avoid any potential reaction in this patient?

A. Continue levothyroxine 150 mcg because the patient has been taking the medication.
B. Change the patient to levothyroxine 50 mcg and have her take 3 tablets daily.
C. Change the patient to intravenous formulation and have her receive 1-mg weekly injections.
D. Change the patient to levothyroxine 50 mcg and have her take 21 tablets weekly.

31. A 25-year-old woman with thyroidectomy is initiated on levothyroxine 112 mcg daily. She has no other significant medical history. She takes a prenatal multivitamin and ferrous sulfate daily. Which one of the following counseling points is best to give this patient?

A. Take levothyroxine each morning 1 hour after breakfast to increase absorption.
B. Separate levothyroxine from iron and multivitamin because of impaired absorption.
C. Have a repeat TSH laboratory test in 1 week to assess efficacy and need for dose changes.
D. Take levothyroxine each evening 1 hour after dinner to avoid inconvenience.

32. A 68-year-old man has difficulty remembering to take his levothyroxine 50-mcg tablet every day, despite using a pill container reminder. His daughter, who fills his pill container, usually brings him dinner three times weekly. Which one of the following is best to recommend regarding levothyroxine administration for this patient?

A. 50 mcg three times weekly
B. 175 mcg twice weekly
C. 200 mcg once weekly
D. 300 mcg once weekly

Questions 33 and 34 pertain to the following case.

J.J. is a 40-year-old woman (weight 50 kg) seen in the internal medicine clinic. Her laboratory values include TSH 10 mIU/mL and FT4 0.9 ng/dL. J.J. also has the presence of TPOAb. She has a small goiter but no complaints.

33. Given her laboratory test results and physical examination findings, which one of the following best describes J.J.'s thyroid disorder?

A. Primary hypothyroidism
B. Central hypothyroidism
C. Subclinical hypothyroidism
D. Hashimoto thyroiditis

34. Which one of the following is best to recommend as initial treatment for J.J.?

A. No treatment
B. Levothyroxine 50 mcg once daily
C. Levothyroxine 100 mcg once daily
D. Desiccated triiodothyronine (T3)/T4 1 grain once daily

35. A patient (weight 80 kg) is in the ED with altered mental status, hypercapnia, hyponatremia, and hypothermia. The patient is thought to have myxedema coma. Which one of the following is best to initiate for this patient?

A. Intravenous 200-mcg loading dose of levothyroxine
B. Oral 200-mcg loading dose of levothyroxine
C. Intravenous 125-mcg loading dose of levothyroxine
D. Oral 125-mcg loading dose of levothyroxine

36. A 55-year-old man with bipolar disorder recently began taking lithium after his symptoms failed to respond to several other agents. Titers for antithyroid antibodies were positive. Which one of the following is the strongest predictor for lithium-induced hypothyroidism in this patient?

A. Older age at therapy initiation
B. Sex
C. Positive antithyroglobulin antibodies titer
D. Higher lithium dose

37. An 18-month-old boy (weight 10 kg) recently received a diagnosis of hypothyroidism. Which one of the following levothyroxine doses is best to recommend for this patient?

A. 12.5 mcg
B. 25 mcg
C. 50 mcg
D. 100 mcg

38. A 27-year-old woman who has had hypothyroidism for several years recently confirmed that she is 4 weeks pregnant. For more than 3 years she has been stable on 75 mcg of levothyroxine once daily. A follow-up appointment with the obstetrician is scheduled in 3 weeks, and she will have thyroid function tests at that visit. Which of the following is best to recommend as an immediate adjustment to this patient's levothyroxine dose?

A. No dose changes until her appointment.
B. No dose changes until her second trimester.
C. Increase levothyroxine to 100 mcg daily.
D. Increase levothyroxine to 150 mcg daily.

39. Which one of the following laboratory tests would best assess thyroid function in a critically ill, hospitalized patient?

    A. TSH
    B. Free thyroxine (FT4)
    C. T3
    D. Reverse T3

40. An elderly woman was initiated on levothyroxine 25 mcg once daily 6 weeks ago. Her laboratory values today show that she still has not achieved a euthyroid status. Which one of the following is best to recommend regarding this patient's levothyroxine?

    A. Continue current dose and repeat thyroid function tests in 2 weeks.
    B. Continue same dose and repeat thyroid function tests in 4 weeks.
    C. Increase dose to 50 mcg once daily and repeat thyroid function tests in 4–6 weeks.
    D. Increase dose to 75 mcg once daily and repeat thyroid function tests in 4–6 weeks.

Learner Chapter Evaluation: Hypothyroidism.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

19. The content of the chapter met my educational needs.
20. The content of the chapter satisfied my expectations.
21. The author presented the chapter content effectively.
22. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
23. The content of the chapter was objective and balanced.
24. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
25. The content of the chapter was useful to me.
26. The teaching and learning methods used in the chapter were effective.
27. The active learning methods used in the chapter were effective.
28. The learning assessment activities used in the chapter were effective.
29. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

30. Demonstrate an understanding of the physiology of the thyroid gland and etiology of hypothyroidism and subclinical hypothyroidism.
31. Analyze a patient profile to identify potential drug-induced causes of hypothyroidism.
32. Develop and/or modify a treatment plan, including monitoring and patient counseling, for a patient with hypothyroidism or subclinical hypothyroidism.
33. Evaluate complications associated with inadequate treatment and over supplementation of thyroid hormones.
34. Distinguish clinical presentation and/or pharmacotherapy requirements in special populations, including pediatrics, pregnancy, elderly, and hospitalized patients.
35. Please provide any specific comments relating to any perceptions of bias, promotion, or advertisement of commercial products.
36. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Questions 37–39 apply to the entire Endocrinology II learning module.

37. How long did it take you to read the instructional materials in this module?
38. How long did it take you to read and answer the assessment questions in this module?
39. Please provide any additional comments you may have regarding this module:

Nephrology I

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Test Waivers: To access the explained answers without submitting a posttest, sign in to your My Account page, select the PSAP book, and click on the waiver link for that module. By completing the waiver form for a module, you waive the opportunity to receive CPE credit for that module. After you submit a waiver, you will see a link to the PDF file that contains the answers for the module you waived. Answers will be available **starting 1 week** after the BCPS test deadline.

Acute Kidney Injury and Dialysis

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LEARNING OBJECTIVES

1. Given a patient's subjective and objective information, evaluate for the risk of an acute kidney injury (AKI).
2. Assess the appropriateness of using certain pharmacologic agents in patients at risk of developing an AKI.
3. Evaluate risk of AKI on the basis of subjective and objective patient information, and recommend appropriate preventive management.
4. Justify drug dosing changes and/or discontinuation in a patient with an AKI.
5. Distinguish the specific components and differences between hemodialysis, peritoneal dialysis, and continuous renal replacement therapy.
6. Evaluate the impact of each type of dialysis on medication dosing and recommendations.

ABBREVIATIONS IN THIS CHAPTER

AIN	Acute interstitial nephritis
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
ATN	Acute tubular necrosis
CHF	Congestive heart failure
CIN	Contrast-induced nephropathy
CKD	Chronic kidney disease
CNI	Calcineurin inhibitor
CRRT	Continuous renal replacement therapy
CVVH	Continuous venovenous hemofiltration
CVVHD	Continuous venovenous hemodialysis
CVVHDF	Continuous venovenous hemodiafiltration
EDD	Extended duration dialysis
FENa	Fractional excretion of sodium
IHD	Intermittent hemodialysis
RIFLE	Risk, injury, failure, loss, and end-stage renal disease
RRT	Renal replacement therapy
SLED	Sustained low-efficiency dialysis
Vd	Volume of distribution

Table of other common abbreviations.

INTRODUCTION

Acute kidney injury (AKI) occurs in up to 15% of hospitalized patients, and these patients have an increased risk of morbidity, mortality, and length of stay and increased hospital costs (Lafrance 2010). A mortality rate of close to 50% has been associated with patients with an AKI (Lafrance 2010). A patient can develop an AKI in the community or hospital setting, which can include medical inpatients or critically ill inpatients. Perceived outcomes are different in these possible settings because patients who develop AKI in the community setting are more likely to recover than are critically ill inpatients (KDIGO 2012). Recognizing patients at high risk of AKI is crucial so that appropriate preventive or management strategies can be used. These preventive measures include avoiding nephrotoxins, closely monitoring drugs that are renally eliminated, and recognizing medications that have toxic metabolites. These recommendations are more easily monitored and implemented in the hospital setting; however, clinicians must still evaluate those who may be at risk as an outpatient. Typically, community-acquired AKIs are less likely to be prevented because the insult is discovered after an exposure; therefore, quick evaluation, diagnosis, and management is important to long-term patient recovery.

ADQI, KDIGO, AND NKF KDOQI GUIDELINES

The Acute Dialysis Quality Initiative (ADQI) group began in 2000 as the process to seek consensus and evidence-based recommendations regarding patients with AKI (Ronco 2001). This initiative is meant to standardize the process of diagnosis, prevention, and treatment of AKI in the critically ill patient; develop consensus

recommendations for best practice; facilitate the establishment of evidence-based guidelines for care, when applicable; and identify questions for future research as well as consider study design options (Ronco 2001). However, not until recently was a standardized definition made for AKI; therefore, a multidisciplinary team approach to evolving clinical recommendations regarding cardiorenal and hepatorenal disease, use of continuous renal replacement therapy (CRRT), and indications for renal replacement therapy (RRT) are important, according to the ADQI recommendations (Ronco 2001).

The definition of AKI by the international Kidney Disease: Improving Global Outcomes (KDIGO) clinical guidelines is supported by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) in its commentary on the KDIGO guidelines. The diagnostic criteria for AKI include (1) an increase in SCr of 0.3 mg/dL or greater within 48 hours, (2) an increase in SCr of 1.5 times or more the patient's baseline that has occurred within the previous week, and (3) a urine volume of less than 0.5 mL/kg/hour for more than 6 consecutive hours (Palevsky 2013; KDIGO 2012). A staging system as part of the RIFLE (risk, injury, failure, loss, and end-stage renal disease) criteria for AKI includes risk, injury, and failure that evaluates SCr and urinary output, as well as a staging system defined by Acute Kidney Injury Network (AKIN) criteria that evaluate the same parameters. The loss and end-stage categories of RIFLE correlate with the need for RRT outside the scope of AKI. Both the RIFLE and the AKIN criteria were used to formulate the adopted global definition of AKI. Each stage includes an assessment of SCr as well as an evaluation of the patient's urinary output.

Both staging systems were developed before the KDIGO guidelines, and the KDIGO-adapted definition uses stems from both the RIFLE and the AKIN criteria. Secondary to the release of the RIFLE criteria, the term *acute renal failure* (*ARF*) has been replaced by *AKI*, which encompasses minor changes in renal markers and urinary output in patients needing RRT (Palevsky 2013; KDIGO 2012). This criterion also allows the inclusion of the patients who may have only functional impairment without actual tubular damage to the kidney; therefore, impairment as well as injury is included in the RIFLE criteria. This classification scheme is clinically relevant secondary to the ability of clinicians to recognize a patient who is at risk of an AKI and intervene early to prevent long-term complications. In addition to the RIFLE criteria, AKIN endorsed the RIFLE criteria with the modification of including small changes in SCr within a 48-hour period, defined as an SCr increase greater than 0.3 mg/dL (Palevsky 2013; KDIGO 2012). The patient's mortality risk increases as the AKI stage increases, and the duration of AKI is associated with an increased mortality risk (Palevsky 2013; KDIGO 2012). The definitions of AKI and chronic kidney disease (CKD) have also been evaluated, and the term *acute kidney disease* (*AKD*) is used for patients who meet the criteria for AKI, OR have a glomerular filtration rate (GFR) less than 60 mL/minute/1.73 m^2 for less than 3 months, or a decrease in GFR by 35% or more, or an increase in SCr by more than 50% for less than 3 months (Palevsky 2013; KDIGO 2012). The key difference between the classification of CKD and that of AKD is as follows: if the decreased GFR or kidney damage is less than 3 months in duration, it is considered AKD, whereas if it is more than 3 months, it is classified as CKD. In addition, a patient who does not fall within the classification scheme of AKI, AKD, or CKD is classified as having no known kidney disease. Figure 1-1 further describes this classification scheme. A further approach to evaluating patients for AKI, AKD, and CKD depends on GFR/SCr, oliguria (defined as urine production less than 500 mL/day), kidney damage (evaluated by urinalysis and imaging), and kidney size. Acute kidney injury encompasses GFR/SCr changes and declining urinary output, AKD includes changes in GFR/SCr and structural kidney damage, and CKD can include all measures of changing GFR/SCr, declining urinary output, structural kidney damage, or small kidney size (Palevsky 2013).

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- A general understanding of the pathophysiology of different causes of renal disease
- The ability to appropriately calculate renal function for the evaluation of injury and purpose of medication dose adjustment
- Medications utilized to manage patients with chronic kidney disease or chronic kidney disease complications
- A general overview of the dialysis process

Table of common laboratory reference values

ADDITIONAL/SUGGESTED READINGS

The following free resources have additional background information on this topic:

- KDIGO. Clinical Practice Guideline for the Acute Kidney Injury. 2012.
- KDIGO. Clinical Practice Guideline for the Acute Kidney Injury. Online Appendices A–F. 2012.
- Palevsky PM, Liu KD, Brophy PD, et al. KDOQI US Commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. Am J Kidney Dis 2013;61:649-72. KDOQI Commentary
- Ronco C, Kellum JA, Bellomo R, et al. Acute Dialysis Quality Initiative (ADQI). Nephrol Dial Transplant 2001;16:1555-8.

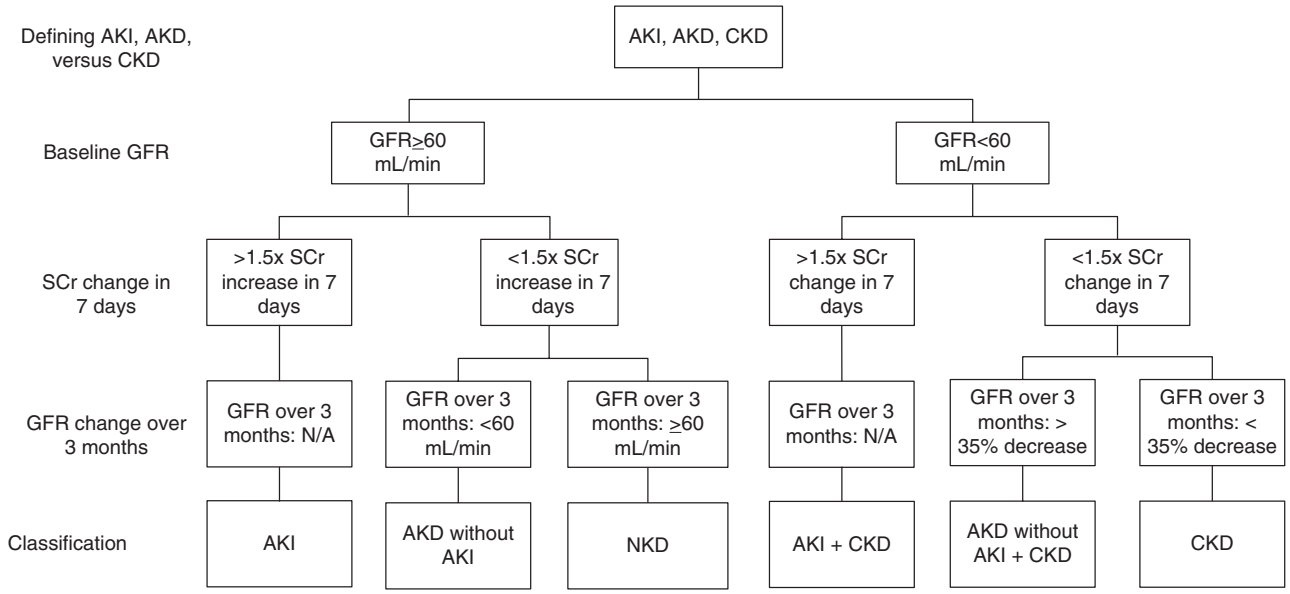

Figure 1-1. Definitions of acute kidney injury, acute kidney disease, and chronic kidney disease classification.

AKI = acute kidney injury; AKD = acute kidney disease; NKD = no known kidney disease.

Information from: Palevsky PM, Liu KD, Brophy PD, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. Am J Kidney Dis 2013;61:649-72; and Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for the Acute Kidney Injury. Kidney Int Suppl 2012;2:1-138.

One of the most difficult issues in appropriately treating patients with AKI is the lack of an accurate and meaningful way to estimate GFR. Because a patient's SCr fluctuates during an AKI and lags in its accumulation, this marker is not the most reliable in adequately assessing renal function in the general, hospitalized, or critically ill patient (Bragadottir 2013; Palevsky 2013; KDIGO 2012). It can take up to 48 hours for SCr concentrations to significantly increase before identifying an AKI, which makes renal function equations, such as the Cockcroft-Gault formula, inaccurate; therefore, it is important to monitor urinary output because a decline in urinary output is often the first and most common sign of an impending injury (Bragadottir 2013; Koyner 2012). Secondary to this dilemma, novel biomarkers without the limitations of SCr (e.g., heavy influence of muscle mass and weight, lag time) are also being studied for clinical assessment of kidney function. These biomarkers will aid clinicians in evaluating the risk of AKI, recognizing kidney damage in the early stages, assessing the severity of AKI, and possibly identifying a patient's susceptibility for injury (Ronco 2016). Specific biomarkers may also allow for the diagnosis of subclinical AKI, despite normal values of common monitoring values, as well as allow the ability to pinpoint the cause and type of renal insult, which will lead to early recognition and initiation of preventive measures (Ronco 2016).

To date, the most successful biomarkers include urinary neutrophil gelatinase-associated lipocalin, cystatin C, interleukin-18 (IL-18), and kidney injury molecule-1 (KIM-1) (KDIGO 2012; Thurman 2008). Neutrophil gelatinase-associated lipocalin has been studied in critically ill patients, specifically those with sepsis. The outcome of a meta-analysis showed the biomarker to be effective in predicting an AKI as well as the need for RRT, leading to a mortality benefit (Zhang 2016). Neutrophil gelatinase-associated lipocalin has also been evaluated in patients undergoing cardiac surgery and is predictive of AKI on the basis of urine and plasma thresholds that have been determined to evaluate the risk and degree of renal injury (de Geus 2016). Investigators have studied cystatin C for years to find its niche in evaluating AKI risk compared with SCr. Mechanistically, cystatin C is produced and released by nucleated cells, which could lead to alterations in its effectiveness in patients with cancer, uncontrolled thyroid disorder, steroid therapy, or rapid cell turnover (Knight 2004). Measuring cystatin C to determine the risk of developing CKD has shown more promise than measuring the SCr in detecting and categorizing reduced kidney function at early stages (Shlipak 2013). This biomarker is more specific to long-term risk associated with CKD. Studies evaluating IL-18 for AKI prediction have determined that this biomarker is more useful and appropriate in the pediatric patient population (Lin 2015). Interleukin-18 has shown promise in predicting an AKI in the adult population; however, the evidence pool is not robust, and a limitation to note is that the pathophysiological mechanism of IL-18 is not completely understood

(Lin 2015). Secondary to this, IL-18 has been elevated in patients with other renal pathophysiology, leading clinicians to use this biomarker to guide diagnosis rather than early AKI prediction (Lin 2015). Finally, KIM-1 has shown promise in evaluating AKI risk, especially after cardiopulmonary bypass surgery in the adult and pediatric populations (Devarajan 2011). Moreover, for patients who have already had an AKI, KIM-1 shows predictive value of the need for RRT and mortality (Devarajan 2011).

Each of these biomarkers is directly associated with the functionality of the proximal tubule by different mechanisms and is more sensitive to fluctuating renal function than SCr. However, despite research advances in this area, drug dosing adjustments are generally based on a CrCl estimation using the Cockcroft-Gault equation. As novel biomarkers become more commonly used in clinical settings, studies of their use for drug dosing are needed (KDIGO 2012; Thurman 2008).

AKI RISK FACTORS AND ETIOLOGY

Identifying the etiology of AKI is important for appropriate management and early intervention. Acute kidney injury is typically classified as prerenal, intrinsic, or postrenal. Prerenal injury correlates with a decreased kidney perfusion; intrinsic injury involves damage to a structure of the kidney; and postrenal injury is an impediment in urinary flow. The type of injury can be identified by evaluating patient-specific criteria. The BUN/SCr ratio helps identify a prerenal versus an intrinsic cause of the AKI. A BUN/SCr ratio greater than 20:1 is associated with prerenal injury, whereas a BUN/SCr ratio of 10:1–20:1 more likely has an intrinsic cause (KDIGO 2012). Another marker of kidney function that helps differentiate the cause of AKI is the fractional excretion of sodium (FENa). The FENa calculation considers urinary sodium, SCr, urinary creatinine, and serum sodium to assess the filtering capacity of the kidneys. A FENa of less than 1% indicates that tubular function within the nephron is still intact and that the sodium-retentive mechanisms in the kidney are being stimulated appropriately. When the definitive characteristics of AKI have been met, a FENa less than 1% correlates with a diagnosis of prerenal AKI (Palevsky 2013; KDIGO 2012). Alternatively, a FENa greater than 2% indicates that patients cannot concentrate their urine, suggesting tubular damage, in which case patients will more than likely have an acute intrinsic kidney injury (KDIGO 2012). Postrenal AKI involves an obstruction, such as cancer, prostate enlargement, or stone, for which a patient will more than likely need surgical intervention. Imaging studies need to be done in this setting because subjective information cannot help classify this etiology. If a patient is receiving diuretic therapy, secondary to its mechanisms and sites of action that affect sodium and water, using FENa will be clinically irrelevant in determining an etiology.

The RIFLE and the AKIN criteria, defined and discussed earlier, have limitations. The biggest limitation is their ability to identify patients with a community-acquired AKI, given that consistent monitoring and a timeline evaluation are difficult to determine. Moreover, SCr and urinary output have limitations in detecting AKI. The novel biomarkers on the horizon may provide a much clearer picture of AKI as well as help identify these patients earlier.

Despite the classification schemes set forth by the KDIGO group, the KDOQI group does not support relying solely on these classification criteria to treat patients because it believes that evidence is insufficient to support their consistent use. The KDOQI commentary regarding the KDIGO AKI guidelines endorses focusing on overall clinical status, identifying the underlying cause of the AKI, evaluating trends in kidney function, assessing pertinent comorbid disease states, assessing volume status, and monitoring for acid-base and electrolyte abnormalities in order to help guide clinicians in evaluating for AKI risk factors or potential etiologies (Palevsky 2013). Identifying a patient at an increased risk of an AKI necessitates early intervention, which entails evaluating a set of risk factors that are largely unknown and not a common practice for clinicians worldwide. Ramifications of not using the criteria and evidence-based practices that have been put into place can lead to lost opportunities to prevent AKI from occurring.

Risk factors that place a patient at highest risk of developing an AKI include age older than 75, preexisting CKD, congestive heart failure (CHF), atherosclerotic peripheral vascular disease, liver disease, diabetes, use of nephrotoxic medications, and decreased volume status (Palevsky 2013; KDIGO 2012; Lewington 2011). These patients should be identified and monitored and preventive strategies initiated, when necessary. In patients at increased risk because of the previously mentioned factors, certain exposures and susceptibility factors place these patients at an even higher risk of developing an AKI (Palevsky 2013; KDIGO 2012). Such factors are difficult to apply to each patient because the susceptibility factors vary from person to person. Exposures that have been associated with nonspecific AKI include sepsis, critical illness, circulatory shock, burns, trauma, cardiac surgery, major noncardiac surgery, nephrotoxic drugs, radiocontrast dye, and poisonous plants and animals (KDIGO 2012). Specific susceptibility factors that can increase a patient's risk of AKI include dehydration/volume depletion; advanced age; female sex; black race; CKD; chronic diseases of the heart, lung, and/or liver; diabetes; cancer; and anemia (KDIGO 2012). Obviously, some of the susceptibility factors are nonmodifiable, and others show up as risk factors themselves, meaning they not only increase a patient's susceptibility for AKI but also have an associated risk (KDIGO 2012).

These are merely guidelines and possible factors that can help a clinician make appropriate, patient-specific monitoring plans. However, the guidelines present a structured way to initiate patient evaluation and assessment of risk factors, exposures, and susceptibility: (1) risk before an exposure to

a kidney insult; (2) risk after an exposure to a kidney insult; (3) risk after developing and recovering from an AKI; and (4) monitoring for delayed sequelae (Palevsky 2013; KDIGO 2012) (Table 1-1).

Management after an AKI develops includes the use of validated scoring systems to aid in predicting a patient's outcome (KDIGO 2012). Many studies have looked at scoring systems that include several different factors; the most validated systems include risk scores in either cardiac or noncardiac surgical procedures (KDIGO 2012; Candela-Toha 2008; Kheterpal 2007). These predictive scoring systems not only aid the clinician in predicting risk of AKI, but also allow for the breakdown of certain subpopulations to permit more specific evaluations. The ultimate goal is to bring patients back to their baseline renal function to minimize their risk of having delayed sequelae; however, this is not always possible. Chronic kidney disease can occur in patients who have had an AKI, and factors that place patients at the highest risk of CKD occurrence include a history of cardiovascular surgery, hemolytic uremic syndrome, and/or exposure to aminoglycosides or radiocontrast dye (Coca 2009). A higher score according to the RIFLE and AKIN criteria, together with the duration of the AKI, also correlates with patient recovery and long-term risk, possibly leading to end-stage renal disease, myocardial infarction, or increased mortality (Coca 2009).

Many of the factors presented in Table 1-1 are unmodifiable. Modifiable susceptibility factors will be discussed in the Prevention of AKI and Management of AKI sections.

Table 1-1. Risk Assessment and Management According to Susceptibility Factors

	Susceptibility Factors
Risk assessment: Before an exposure	• Decreased volume status[a] • Hypoalbuminemia[a] • Advanced age[a] • Female sex[a] • African American race[a] • Previous AKI[a] • CKD[b] • Diabetes[b] • Heart disease[b] • Pulmonary disease[b]
Risk assessment: After an exposure	• Genetic polymorphisms • Genetic mutations
Management: After AKI development	• Validated scoring systems for outcome prediction
Risk assessment: Delayed sequelae	• CKD • Dialysis • Cardiovascular events • Mortality

[a]Susceptibility factors increase the likelihood that a patient's kidney will be vulnerable to injury.

[b]Chronic comorbidities increase susceptibility to AKI.

AKI = acute kidney injury; CKD = chronic kidney disease.

Information from: Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for the Acute Kidney Injury. Kidney Int Suppl 2012;2:1-138.

Pseudo–Drug-Induced Nephropathy

A common saying in clinical practice is to treat the patient, not the number. This holds true in patients with AKI, and in some instances, the patient may have pseudo-AKI induced by laboratory changes as a result of medication therapy. Clinicians should consider the possibility of an erroneous laboratory value or an error in reporting the value, which should be evaluated before initiating therapy for a presumed AKI, especially if a pseudo-AKI is a possibility. Cephalosporins are the specific drug class most associated with in vitro interference with the SCr assay (KDIGO 2012). Triamterene, trimethoprim, cimetidine, and probenecid can lead to the inhibition of SCr secretion into the renal tubules, which can lead to a falsely elevated SCr in a patient taking these medications. Moreover, steroids and tetracyclines can increase a patient's BUN. Together with the drug-specific factors associated with pseudo-AKI, patient-specific factors must be considered. Excessive muscle mass can lead to abnormally high muscle breakdown, such as in bodybuilders or marathon runners, and may be associated with a falsely elevated SCr; in this case, alternative methods of evaluating renal function must be used such as measuring CrCl using 24-hour urine collection, inulin or iothalamate clearance, or cystatin C.

Nephrotoxic Medications

For the pharmacist, recognizing and using appropriate caution when initiating a potentially nephrotoxic medication is important in the high-risk patient with an AKI. It is also important to recognize when certain medications should be dose adjusted, held, or discontinued in the presence of AKI. Moreover, certain renal etiologies are parallel to drug-related causes and should be identified according to the clinical and patient-specific factors surrounding the ultimate diagnosis and etiology of AKI. Some drug-associated risk factors for AKI are not always commonly thought of as potential nephrotoxins; however, if not identified promptly, delay in appropriate AKI treatment and resolution can occur if the medication is not discontinued or if necessary supportive management is not initiated in a timely manner.

Potentially nephrotoxic medications have inconsistent reports throughout drug information resources, guidelines, and published literature regarding the significance and likelihood of AKI induction (Bicalho 2015). In addition, there are

many ways in which a drug can lead to a renal injury, and the most common diagnoses related to drug-induced AKI include intraglomerular pressure alterations, acute tubular necrosis (ATN), chronic or acute interstitial nephritis (AIN), glomerulonephritis, rhabdomyolysis, crystal nephropathy, and thrombotic microangiopathy. Several medications affect more than one pathophysiologic mechanism that can lead to renal harm, and these drugs carry a higher risk of a patient's developing an AKI, especially high-risk patients. These drugs and their pathology are shown in Box 1-1.

PREVENTION OF AKI

The key to preventing an AKI is to establish risk, as discussed in the previous section. Moreover, because patients with an AKI are at risk of significant morbidity and mortality, appropriate preventive measures are crucial in the at-risk patient population. Two areas of greatest impact are hydration perioperatively and radiocontrast dye administration. Hemodynamic status is key to preventing an AKI in patients because renal perfusion is vital in adequately maintaining sustainable pressure for the kidneys to function appropriately. Therefore, maintaining intravascular volume is recommended to sustain a positive fluid balance and adequate kidney perfusion.

Perioperative AKI Prevention

In the perioperative period, there is no specific fluid of choice; rather, patient-specific factors should be evaluated when choosing the most appropriate hydration fluid, flow rate, and monitoring values. Goals of hydration therapy include avoiding hypotension; optimizing oxygen delivery; using vasopressors, inotropic agents, or blood products, if necessary; and ensuring a fine balance between adequate hydration and fluid overload (Palevsky 2013; KDIGO 2012). In the postoperative period, patients typically retain sodium and water secondary to the body's stress response of enhanced secretion of antidiuretic hormone and up-regulation of the renin-angiotensin-aldosterone system; therefore, isotonic saline can lead to fluid overload, possible sodium or chloride excess, or hyperchloremic acidosis (Lewington 2011). Alternatively, dextrose-containing fluids can increase the patient's risk of becoming hyponatremic, and lactated Ringer solution can lead to hyperkalemia, especially for an AKI or a diagnosis of CKD.

Contrast-Induced Nephropathy Prevention

Contrast dye, specifically iodine-based contrast dye used in CT or angiography, has a high likelihood of inducing ATN because of its hyperosmolar property, especially in patients who are hemodynamically unstable. Other risk factors for developing contrast-induced nephropathy (CIN) include having other nephrotoxic medications on board or having a diagnosis of CKD, diabetes, or CHF. The importance of hydration, specifically normal saline, in this setting cannot be overestimated because it restores or maintains intravascular volume

Box 1-1. Association of Pathophysiologic Insult with Medication Therapy

Acute interstitial nephritis

- Acyclovir
- Allopurinol
- β-Lactam antibiotics[a]
- Fluoroquinolones
- Indinavir
- Lansoprazole
- Loop diuretics
- NSAIDs
- Omeprazole
- Pamidronate
- Pantoprazole
- Phenytoin
- Ranitidine
- Rifampin
- Sulfonamides
- Thiazide diuretics
- Vancomycin[a]

Acute tubular necrosis

- Adefovir
- Alendronate
- Aminoglycosides[a]
- Amphotericin B[a]
- Cidofovir
- Cisplatin
- Contrast dye[a]
- Foscarnet
- Pentamidine
- Tenofovir

Chronic interstitial nephritis

- Acetaminophen[a]
- Aspirin[a]
- Carmustine
- Cisplatin
- Cyclosporine[a]
- Lithium
- NSAIDs

Crystal nephropathy

- Acyclovir
- Ciprofloxacin
- Foscarnet[a]
- Ganciclovir[a]
- Indinavir[a]
- Methotrexate
- Sulfonamides[a]
- Triamterene

Glomerulonephritis

- Ampicillin
- Gold
- Interferon alfa
- Lithium[a]
- NSAIDs[a]
- Pamidronate
- Penicillin

Intraglomerular pressure alterations

- ACEI[a]
- ARB
- Canagliflozin
- Dapagliflozin
- Cyclosporine
- NSAIDs[a]
- Tacrolimus

Thrombotic microangiopathy

- Clopidogrel[a]
- Cyclosporine
- Mitomycin-C
- Quinine
- Ticlopidine[a]

[a]The most common offending medications for pathophysiologic insult.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.

Information from: Bicalho MD, Soares DB, Botoni FA, et al. Drug-induced nephrotoxicity and dose adjustment recommendations: agreement among four drug information sources. Int J Environ Res Public Health 2015;12:11227-40; and Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for the Acute Kidney Injury. Kidney Int Suppl 2012;2:1-138.

in order to minimize tubular obstruction, vasoconstriction, or ischemia by diluting the contrast media reaching the kidney. International guidelines recommend using either normal saline or isotonic sodium bicarbonate as hydration fluid; however, data suggest that hydration with 0.9% normal saline 1 mL/kg/hour 12 hours before and 12 hours after contrast administration in high-risk patients is more effective than isotonic sodium bicarbonate, which was initially thought to alkalinize the urine and decrease the production of oxygen free radicals (Subramaniam 2016; Palevsky 2013; KDIGO 2012). If isotonic sodium bicarbonate is used, 3 mL/kg/hour is recommended 1 hour before and 6 hours after contrast administration (Palevsky 2013). Whichever hydration fluid is chosen, cardiac, pulmonary, and hemodynamic stability must be monitored closely to avoid fluid overload, specifically in patients with CHF. More aggressive preventive strategies are necessary in patients at highest risk, according to the risk factors mentioned earlier, who have a CrCl less than 60 mL/minute/1.73 m^2 or an SCr greater than 1.5 mg/dL or in patients receiving high-osmolar contrast media (Mehran 2009; Choyke 1998; Deray 1996). Antioxidants and statins have also been studied in combination with hydration for their ability to prevent CIN. Because antioxidants can decrease the oxidative stress associated with oxygen free radicals, they can possibly prevent CIN in high-risk patients. The most widely used antioxidant with the most proven efficacy in high-risk patients is acetylcysteine at much lower doses than those used for acetaminophen toxicity (Palevsky 2013; KDIGO 2012). The recommended acetylcysteine dosage for CIN prevention is 600–1200 mg orally twice daily on the day before contrast administration and 600–1200 mg orally twice daily on the day afterward for four doses total. If this is not feasible secondary to an acute or urgent situation, 600–1200 mg of acetylcysteine can be given within 4 hours of contrast administration (Palevsky 2013; KDIGO 2012). Acetylcysteine can be given as intravenous boluses at equivalent doses if the oral route is not feasible; however, the risk of anaphylaxis using intravenous dosing is higher than the risk of using oral acetylcysteine. The mechanism of using statin therapy for CIN prevention involves the ability of this class of agents to stabilize the endothelium as well as to act as oxygen free radical scavengers (Subramaniam 2016). Statin therapy, in particular, has been studied in CIN prevention surrounding cardiovascular surgery, including percutaneous coronary intervention, with atorvastatin as the most common statin studied (Subramaniam 2016). Adenosine antagonists and ascorbic acid have also been studied in CIN prevention, but results of their benefit have been conflicting. The most promising agents used for the prevention of CIN are hydration with normal saline plus acetylcysteine, with or without statin therapy (Subramaniam 2016).

Specific guideline-recommended nephrotoxic agents to hold 24–48 hours before contrast administration in a high-risk patient include NSAIDs, diuretics, aminoglycosides, amphotericin B, acyclovir, and foscarnet (KDIGO 2012). Although not listed in the guidelines, there is an FDA alert for discontinuing metformin before contrast administration if a patient's GFR is 30–60 mL/minute/1.73 m^2 or if the patient has a history of liver disease, alcoholism, or heart failure; will receive intra-arterial iodinated contrast; is 75 years or older, has hypovolemia, and/or will receive high volumes of iodinated contrast (NICE 2013). According to the American College of Radiology, metformin should be held in patients with an AKI, stage 4 or 5 CKD, or a GFR less than 30 mL/minute/1.73 m^2 and if patients are undergoing arterial catheter studies (ACR 2016). Metformin does not lead to or increase the risk of CIN, but it can increase a patient's risk of developing lactic acidosis if CIN occurs. Monitoring after contrast administration is crucial because SCr can begin increasing within 48 hours and peak as far out as 5 days if a patient ends up having an AKI (Palevsky 2013; KDIGO 2012). By closely following a high-risk patient after contrast administration, pharmacists can manage AKI early on, and angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) use can be discontinued if the SCr increases by at least 30% of the patient's baseline. Metformin can be held or discontinued if the SCr increases to greater than 1.4 mg/dL in females or greater than 1.5 mg/dL in males, as defined in the package insert. Alternatively, according to more recent literature, the decision can be made using the patient's CrCl value (Lewington 2011). Once a patient is treated appropriately and renal function either returns to baseline or has a new baseline, the ACEI or ARB can be reinitiated because these have renoprotective properties in patients with CKD or diabetes. Metformin reinitiation will depend more on clinical judgment, patient-specific factors, and evaluation of recent literature. In patients receiving contrast in the outpatient setting, most of the aforementioned strategies are not feasible. For some patients, recent laboratory measurements may not be available for the clinician to assess renal function. Moreover, when such measurements are not practical or feasible, questionnaires have been validated and used to identify patients who may be at high risk of AKI. These questionnaires allow patients to answer questions regarding their medical history that would place them at an increased risk of AKI, including diabetes, kidney disease, and hypertension, as well as questions that focus on self-reporting previous studies that use contrast (KDIGO 2012).

Types, doses, and osmolarity of contrast media have been studied to evaluate whether they contribute to AKI risk. Comparison of agents is shown in Table 1-2. Iodine-based contrast agents, which are mainly used for angiography, radiography, or CT scans, are associated with a higher risk of developing CIN if the ionic form is used (Mehran 2009; Choyke 1998; Deray 1996). Typically, this contrast dye is either ionic or nonionic, with the nonionic, or organic, form leading to fewer complications secondary to its ability to limit the exposure to iodine molecules (Rudnick 1995). The correlation of contrast

Table 1-2. Comparison of Iodinated Contrast Media

Subgroups	High-Osmolar Contrast Media	Low-Osmolar Contrast Media		Iso-osmolar Contrast Media
		Nonionic	Ionic	Nonionic
Agents	Diatrizoic acid Iothalamate	Iohexol Iopamidol Ioversol Iobitridol	Ioxaglate	Iodixanol
Iodine atoms: Molecule[a]	1.5:1	3:1		6:1

[a]Also defined as ratio agents, which is the ratio of iodine atoms contained in a molecule to the osmotically active particles produced by the molecule in solution; therefore, fewer total molecules are needed to provide adequate amounts of iodine for imaging procedures.

Information from: Deray G, Jacobs C. Are low osmolality contrast media less nephrotoxic? Nephrol Dial Transplant 1996;11:930-1; and Solomon R. Contrast Media: Are There Differences in Nephrotoxicity Among Contrast Media? BioMed Research International. January 22, 2014;ID 934947:8 pages.

dye with AKI is dose-dependent; therefore, higher doses of the agent are associated with an increased risk of CIN (Palevsky 2013; KDIGO 2012). Osmolarity also correlates with renal morbidity; higher-osmolarity contrast media are associated with increased rates of CIN because of the significantly higher risk of renal vasoconstriction (Roh 2015; KDIGO 2012; Deray 1996). In patients at high risk of developing an AKI, it is recommended to use low-osmolar or iso-osmolar contrast dye. Of note, even if a contrast dye is considered "low" osmolar, its osmolarity is twice that of human serum, and "iso" osmolar has an osmolarity that is about equivalent to human serum (ACR 2016). The only iso-osmolar, nonionic contrast medium in the United States is iodixanol (Visipaque); however, the potential benefit of less risk of an AKI comes with a higher cost (KDIGO 2012). Clinicians must use clinical judgment and patient-specific factors to determine the most appropriate agent, according to osmolarity, risk factors, and cost. Ioxaglate (Hexabrix) is an ionic low-osmolar contrast media, which would be less than ideal to use in a patient at risk of developing an AKI because of its ionic component. Iohexol (Omnipaque), iopamidol (Isovue), and ioversol (Optiray) are nonionic, low-osmolarity contrast agents theorized to be best for use in patients who are at a higher risk of developing CIN (Roh 2015; KDIGO 2012; Deray 1996). The benefit of using nonionic low-osmolar contrast media in high-risk patients needing imaging studies compared with using iodixanol is unclear (Roh 2015; Deray 1996). Ultimately, preventive measures should be taken in high-risk patients, especially those who will receive high-volume, high-dose, and/or osmolar agents.

Gadolinium-based contrast agents, which are commonly used for MRI, can lead to a rare adverse effect in patients with underlying kidney disease known as nephrogenic systemic fibrosis (NSF), defined by hardening and fibrotic changes of the skin and internal organs (Cowper 2013). Gadolinium-based agents do not cause CIN, but they can cause NSF in vulnerable patients.

AKI Prevention in Patients with Rhabdomyolysis

Preventive measures for AKI should also be initiated in patients with rhabdomyolysis. Hydration with 0.9% sodium chloride or sodium bicarbonate is recommended as the fluid modality. In rhabdomyolysis, myoglobin is filtered by the kidneys, and the tubule epithelial cells can directly be affected because myoglobin is toxic to this portion of the kidney. Specific volume expansion guidelines for patients with rhabdomyolysis include aggressive hydration with 0.9% sodium chloride at 10–15 mL/kg/hour to improve the urinary output to a goal of at least 100 mL/hour. Acidotic patients with a diagnosis of rhabdomyolysis have an increased risk of developing an AKI, so sodium bicarbonate can be added to the maintenance fluid to maintain a urinary pH greater than 6.5 (Lewington 2011).

Nephrotoxic Medications

Hemodynamically mediated AKI is secondary to alterations in intraglomerular pressure caused by either drug therapy or decreased perfusion.

Increased doses of ACEIs and ARBs with increased SCr concentrations are typically self-limiting because these drugs cause vasodilation of the efferent arteriole, thus leading to decreased intraglomerular pressure and increased SCr values. Once the kidneys respond to this change, SCr concentrations will normalize within 2–3 weeks after therapy initiation. After initiation of these agents or a dosage change, it is crucial to follow up within 1 week to ensure that the patient's SCr has not increased more than 30% from baseline (Lewington 2011). If a patient's SCr increases more than 30% after initiation or

a dosage increase, the medication should be discontinued (Palmer 2003). Because these drugs are especially important for use in patients with CKD and diabetes, preventive measures can be used to help minimize the risk of ACEI- and ARB-induced nephrotoxicity. The main preventive measures, in this case, are to avoid concomitant diuretic use, if possible, when initiating these agents, as well as to start at low doses and titrate slowly until the patient-specific goal has been reached. Specific risk factors to be aware of that increase a patient's susceptibility for ACEI or ARB nephrotoxicity include bilateral renal artery stenosis, decreased renal blood flow, and a preexisting diagnosis of CKD (Palevsky 2013; KDIGO 2012).

Nephrotoxicity with NSAIDs can present with decreased urinary output; elevations in SCr, BUN, and potassium; and fluid retention with concomitant weight gain. The mechanism of action of NSAIDs is cyclooxygenase-1 and 2 inhibition that results in prostaglandin synthesis. The prostacyclin derivatives of prostaglandins are vasodilators; therefore, with the decrease in prostaglandin synthesis, vasoconstriction can occur, which can lead to elevated blood pressure as well as vasoconstriction of the afferent arteriole, which decreases renal perfusion. Nephrotoxicity with NSAIDs is different from AIN. Patients at highest risk of NSAID nephrotoxicity are those with a diagnosis of CKD, those receiving concomitant diuretic therapy, and older adults (Palevsky 2013; KDIGO 2012). In patients who are at an increased risk of developing an AKI, use of an ACEI or ARB in combination with an NSAID can lead to decreased intraglomerular pressure secondary to the vasoconstriction of the afferent arteriole and the vasodilation of the efferent arteriole, thereby leading to inadequate pressure for the kidneys to function properly. Ultimately, this combination of therapy, especially with the use of NSAIDs chronically, should be avoided in the at-risk patient population. The primary preventive strategy to avoid NSAID nephrotoxicity is to use alternative therapies for pain management. If an NSAID is indicated or necessary, sulindac is the NSAID of choice because it affects prostaglandin synthesis to a lesser extent than the other NSAIDs (Lewington 2011).

Calcineurin inhibitor (CNI) nephrotoxicity, specifically with cyclosporine and tacrolimus, can occur within days of initiating therapy. This dose-related effect leads to vasoconstriction of both the afferent and efferent arterioles, which can lead to decreased renal perfusion and a decline in GFR. This class of medications, with cyclosporine having a more significant adverse effect of nephrotoxicity than tacrolimus, makes it difficult to identify whether it is appropriate to use a CNI in the transplant recipient as well as to differentiate between nephrotoxicity and acute rejection of the transplanted organ (Palevsky 2013; KDIGO 2012). The CNI nephrotoxicity can present within days of initiating therapy, with the increase in SCr as one of the first signs. Other signs of CNI nephrotoxicity include blood pressure much higher than the patient's baseline and alterations in potassium and magnesium concentrations, specifically hyperkalemia and hypomagnesemia (Naesens 2009; De Mattos 2000). Some of the biggest risk factors for CNI toxicity are elevated CNI concentrations related to higher doses of these medications, the presence of other nephrotoxins, and a history of a kidney transplant. To minimize the risk of CNI nephrotoxicity, consistent monitoring of serum concentrations is recommended, as is using combination immunosuppressive therapy to use lower doses when combined with other nonnephrotoxic immunosuppressive agents. The CNIs can also cause nephrotoxicity that is non–dose-dependent, which presents as interstitial fibrosis. Although outside the scope of this chapter, CNIs are not just associated with AKI because they can also cause CKD that is irreversible compared with acute CNI-induced AKI. Dihydropyridine calcium channel blockers, specifically nifedipine, may also be used to antagonize the vasoconstrictor effects of the CNI (Naesens 2009).

Acute tubular necrosis is the most common type of intrinsic AKI and is most associated with the use of nephrotoxic drug therapy as well as prolonged ischemia. This typically occurs with a quick decline in a patient's renal function that can continue to worsen over 2 weeks. The SCr and BUN will increase rapidly, and the patient's urinary output will typically decrease. The specific agents most likely to cause ATN are discussed in the text that follows.

Aminoglycoside nephrotoxicity presents as a slow increase in SCr with an obvious decline in CrCl after about 7 days of therapy. In patients at a higher risk of developing an AKI, signs and symptoms of renal injury may appear earlier than 1 week. Inappropriate dosing of aminoglycosides is one of the risk factors, as well as one of the best ways to prevent an aminoglycoside-induced AKI. Large cumulative doses over an extended period, elevated trough concentrations, or recent aminoglycoside administration can lead to an increased risk of developing an AKI (Matzke 2011; Matzke 2008). The best preventive strategy is to avoid aminoglycosides in high-risk patients; however, this is not always possible, depending on the type of infection treated as well as the culture and susceptibility report. If avoiding aminoglycoside therapy is not an option, maintaining adequate hydration; limiting total cumulative dose; using extended-interval dosing, if appropriate; and providing frequent monitoring and dosage adjustments as needed are the best methods to prevent an AKI (Matzke 2011). Another option is to administer aminoglycosides locally to prevent AKI (e.g., using inhalation aminoglycoside therapy for patients with pneumonia).

Amphotericin B nephrotoxicity can begin to appear at cumulative doses of about 2–3 g of the conventional product. Typical amphotericin B doses are weight based and, depending on the indication, average 0.5–1.5 mg/kg/day for conventional dosing and 3–5 mg/kg/day for the lipid complex (Matzke 2011). Conventional and liposomal formulations of amphotericin B can also affect the extent of renal damage. Use of the liposomal product is recommended in high-risk patients (Palevsky 2013; KDIGO 2012). Risk factors that increase the susceptibility of high-risk patients

are high daily and cumulative doses, as well as rapid infusion of the medication. Preventive measures include avoiding other nephrotoxins, if possible, during amphotericin B therapy; trying to limit the cumulative dose; and keeping the patient well hydrated to ensure adequate kidney perfusion. With advances in medication therapy over the previous years, many other options are available for managing fungal infections, including echinocandin therapy as well as azole antifungals, thus limiting the use of amphotericin B (Plevsky 2013; KDIGO 2012).

With the platinum agents cisplatin and carboplatin, nephrotoxicity presents about 2 weeks after initiation of therapy and is accompanied by hypomagnesemia secondary to renal magnesium wasting (Matzke 2011). An important risk factor in the nephrotoxicity of the platinum agents is administration of subsequent doses in combination with renal radiation therapy. When using these agents, it is important to hydrate the patient before drug administration and to use the smallest dose and frequency for the specific indication.

MANAGEMENT OF AKI

Once a patient has had an AKI, management strategies must be initiated early. The main and most important goal is to have the patient's kidney function return to baseline. To do this successfully, the clinician should be diligent in ensuring that further renal insults are eliminated or minimized, extrarenal complications are being monitored for and managed as necessary, potential causes are evaluated, appropriate treatment for the underlying etiology is initiated, and early intervention is initiated to speed up the recovery process. Recognizing the pharmacokinetic changes that occur in patients who have an AKI helps ensure that appropriate drug dosing is implemented in order to prevent adverse drug events, especially in the critically ill population (Matzke 2008). Obviously, decreased renal clearance of drugs, toxins, or active drug metabolites occurs in AKI because of decreases in glomerular filtration, tubular secretion, and renal metabolism, but there is also evidence that nonrenal clearance can be altered in patients who have an AKI (Vilay 2008). As renal clearance diminishes, drugs that are substrates of P-glycoprotein or the CYP system may be affected. In addition, increases in volume of distribution (Vd) can occur within 24–48 hours secondary to changes in protein and tissue binding as well as in fluid overloaded patients; therefore dosage recommendations for patients with CKD should be used in patients who have had an AKI (Matzke 2008; Vilay 2008). With this knowledge, the clinician can evaluate drug dosage, response, effectiveness, and toxicity, even if a drug is not primarily eliminated by the kidney. Moreover, to ensure minimal adverse drug effects, the clinician must be aware of the drugs that have active or toxic metabolites because these drugs may require dosage adjustment and additional monitoring. An overview of drugs with active metabolites appears in Table 1-3. Finally, knowing how RRT can affect the renal and nonrenal clearance of drugs is important when making dose adjustments according to patient-specific response and factors, to be discussed later in the chapter. However, information regarding appropriate drug dosing in a patient with AKI is not readily available for most medications because studies have not determined all the factors in such a dynamic disease.

Management of Prerenal AKI

The main cause of prerenal AKI is decreased renal perfusion; therefore, the main intervention is hydration. Decreased renal perfusion can be drug induced or can occur because of dehydration, low blood pressure, sepsis, CHF exacerbation, or blood loss. The biggest culprits are drugs specifically related to hemodynamically mediated AKI that alter pressure in the kidneys secondary to vasoconstriction of the afferent arteriole. Treating the underlying cause or removing a culprit drug seems like a commonsense approach, but initiating antibiotics for sepsis and fluid and/or vasopressors for hypotension, for example, may not be the only intervention necessary for managing a prerenal AKI. After evaluating the objective information, an intravenous fluid challenge with 250–500 mL of 0.9% normal saline should be initiated, followed by an assessment of volume status and urinary output, using special caution with fluid administration in patients with CHF (Palevsky 2013; KDIGO 2012). Urinary output is especially important because if a patient does not make urine in response to a fluid challenge, the patient may become fluid overloaded. In patients with any kidney injury, there is a fine balance between hydration and fluid overload, especially in patients with CHF; therefore, monitoring for pulmonary edema, peripheral edema, changes in blood pressure and urinary output, and electrolyte balance is crucial during the early stages of volume expansion. In patients with a prerenal acute or chronic kidney injury, the balance of hydration is even more crucial because they already have a diagnosis of CKD. In this instance, slower rehydration of the patient is recommended, and the same monitoring values should be used. In patients who remain hypotensive despite fluid challenges, initiating vasopressors or inotropes may be necessary. In addition, if a patient has decreased renal perfusion secondary to acute blood loss, packed RBCs should be transfused to restore perfusion (Lewington 2011). Initiating fluid is a second-line recommendation because blood volume resuscitation and recovery of hemoglobin and hematocrit concentrations are crucial.

In a patient who has had an intrinsic AKI, interventions and therapies should be targeted at preventing further renal insults. The three main types of intrinsic kidney injury are ATN (discussed previously), acute glomerulonephritis, and AIN (Matzke 2008; Vilay 2008). Acute glomerulonephritis can be caused by autoimmune diseases or by bacterial or viral infections that lead to damage of the

Table 1-3. Selected Drugs with Active or Toxic Metabolites with Monitoring Values

Drug	Active Metabolite	Effects
Allopurinol	Oxypurinol	Immune-mediated hypersensitivity reaction
Codeine	Norcodeine Morphine	CNS and/or respiratory depression
Dolasetron	Hydrodolasetron	QT prolongation ECG changes
Meperidine	Normeperidine (T)	Neurologic changes
Midazolam	1-Hydroxymidazolam 1-Hydroxymidazolam glucuronide	Sedation/lethargy
Morphine	Morphine-6-glucuronide	CNS and/or respiratory depression
Mycophenolate mofetil Mycophenolic acid	Inactive glucuronide[a]	Leukopenia
Procainamide	Acetylprocainamide (T)	QT prolongation Sinus bradycardia/node arrest
Quinidine	3-Hydroxy quinidine	QT prolongation
Acetaminophen	*N*-acetyl-*p*-benzoquinoneimine (T)	Liver toxicity
Chlordiazepoxide	Oxazepam	CNS effects, including ataxia and confusion
Doxorubicin	Doxorubicinol	Arrhythmias
Oseltamivir	Oseltamivir carboxylate	Severe nausea/vomiting Dehydration
Propranolol	4-Hydroxy propranolol	Bradycardia
Prednisone	Prednisolone	Blood pressure CNS alterations (mood, personality, etc.)
Rifampin	Desacetyl rifampin	Thrombocytopenia CNS effects

[a]Although inactive, glucuronide can displace MPA from albumin, leading to increased free drug concentrations.

(T) = toxic.

Information from: Matzke GR, Dowling TC. Dosing concepts in renal dysfunction. In: Murphy JE ed. Clinical Pharmacokinetics, 4th ed. Bethesda, MD: American Society of Health-System Pharmacists, 2008:427-45; and Vilay AM, Churchwell MD, Mueller BA. Clinical review: drug metabolism and nonrenal clearance in acute kidney injury. Crit Care 2008;12:235.

glomeruli (Matzke 2011). Acute glomerulonephritis is usually associated with an abnormal immune response and can be characterized by hematuria, proteinuria, elevated blood pressure, and/or edema. An acute allergic interstitial nephritis (AIN) is an AKI that originates most commonly because of drug hypersensitivity, with β-lactam and NSAID use usually associated with patients who receive this diagnosis. Patients will present with signs of AKI concomitantly with symptoms such as fever, rash, eosinophilia, pyuria, hematuria, or proteinuria. A common misconception regarding AIN is that previous tolerance of medications can rule out this diagnosis. However, this diagnosis is a diverse condition that varies in possible etiology, presentation, laboratory values, and outcomes (KDIGO 2012; Michel 1998). When many variables must be considered regarding a patient's AKI etiology, AIN is often overlooked, especially in the absence of fever, rash, or eosinophilia (KDIGO 2012; Michel 1998).

Signs and symptoms associated with AIN caused by β-lactams, specifically penicillins and cephalosporins, typically present about 1–2 weeks after initiating the drug; however, early presentation within days of drug administration is possible. Most of these patients will only have signs of pyuria, hematuria, or proteinuria, and less than 30% will have fever, rash, or eosinophilia. Alternatively, NSAID-induced AIN has a delayed onset of signs and symptoms that typically take up to 6 months or longer to appear. Patients most susceptible to NSAID-induced AIN are older adults who have received long-term or chronic NSAID treatment. Compared with β-lactam–induced AIN, NSAID-induced AIN is more commonly

associated with a symptomatology that includes proteinuria as well as the extrarenal signs of fever, rash, and eosinophilia (KDIGO 2012; Michel 1998). These patients will present with a mixed array of signs and symptoms, together with elevated SCr and BUN values indicative of AKI, but the true gold standard for diagnosing AIN is a renal biopsy. Because this is a very invasive test, however, if AIN is suspected, the first-line intervention is to discontinue the perceived offending agent. If a definitive diagnosis of AIN has been made and the patient has no signs of clinical improvement, pharmacologic therapy is warranted. The ideal dose and duration of steroids also depend on patient-specific factors, presence of interstitial fibrosis, and duration of azotemia, if present. If the patient's AIN has progressed to this point, higher doses of steroids for a longer duration have been recommended – most commonly, prednisone 1 mg/kg orally for 4 weeks with a gradual taper over 3–4 weeks to avoid cortisol deficiency caused by hypothalamic-pituitary-adrenal axis suppression (KDIGO 2012; Michel 1998). A discussion of AIN appeared earlier in the chapter under the discussion of AIN most commonly associated with β-lactams or NSAIDs.

Ultimately, there is no recommendation for pharmacologic interventions in patients who have had an AKI other than using supportive measures and treating the underlying cause. Pharmacotherapy for the management of AKI was once recommended to be loop diuretics, dopamine, or fenoldopam (Palevsky 2013; KDIGO 2012). However, no data have supported that these agents provide a clinical benefit in the prevention or management of AKI. Important areas in which loop diuretics are recommended for AKI consist of when patients are fluid overloaded or if they have reached the point of diuretic resistance. Many of these patients also have a concomitant diagnosis of CHF. The most common reason for diuretic resistance that fits the scope of this chapter is ATN, when an overall decrease in the number of functioning nephrons leaves loop diuretics with fewer places to "do their job." The more significant the stage of AKI, the more likely that higher doses of diuretics will be needed in order to exert their effect at the site of action. Patient-specific factors should be considered when choosing the most appropriate diuretic, including drug, dose, and schedule. The least potent loop diuretic is furosemide, which is the most commonly used diuretic secondary to its low cost, safety profile, and ability to be administered both intravenously and orally. However, in a patient with significant diuretic resistance, higher furosemide doses may be necessary, which can lead to significant adverse effects, including ototoxicity. If given orally, furosemide has inconsistent bioavailability, which is inconvenient for a clinician trying to assess response to a certain dose in AKI. Torsemide is more potent than furosemide; however, its use is limited in AKI because its longer duration of action does not lend itself to dose titration. Torsemide also has better and more predictable oral bioavailability than furosemide. Finally, the most potent loop diuretic available is bumetanide. Bumetanide can be given intravenously or orally, has better oral bioavailability than furosemide, and has a lower risk of ototoxicity if higher doses are needed to overcome diuretic resistance. Loop diuretic equivalency doses are shown in Table 1-4. Continuous infusions of loop diuretics may be another way to overcome diuretic resistance because the peaks and troughs of intermittent dosing are eliminated and the risk of adverse drug effects thus minimized. Mechanistically, continuous infusions have an increased rate of sodium and water excretion, and the recommended furosemide dosage in this patient population is a loading dose of 40–80 mg intravenously followed by the infusion of 10–20 mg/hour (Palevsky 2013; KDIGO 2012). Ethacrynic acid is recommended in certain patients with a sulfa allergy.

Like therapy with loop diuretics, dopamine therapy has not been proven to prevent or treat AKI. A low-dose dopamine infusion (1–3 mcg/kg/minute) theoretically improves renal perfusion in the generalizable population secondary to increased natriuresis and diuresis; however, this mechanism has not proven true in patients with AKI and has in fact been associated with worsening renal perfusion in this patient population (Palevsky 2013; KDIGO 2012). In addition, its lack of efficacy and adverse effects, including arrhythmias, QT prolongation, myocardial ischemia, and gangrene/tissue necrosis, can preclude its use for the prevention and management of AKI (Palevsky 2013). However, fenoldopam, a selective dopamine A_1 receptor agonist, has shown more promise in reducing mortality and the need for RRT when initiated early in critically ill patients (Landoni 2007). Low-dose fenoldopam at 0.1 mcg/kg/minute has been studied, but guidelines currently do not routinely recommend use because of minimal supportive studies as well as the risk of hypotension, which could worsen AKI (Landoni 2007).

Medication Use in AKI

As discussed previously, pharmacokinetic and pharmacodynamic principles change in patients with AKI; however, current knowledge is often extrapolated from the pharmacokinetic/pharmacodynamic changes in patients with CKD

Table 1-4. Loop Diuretic Equivalencies

Drug	Equivalent Dosage (IV or PO), mg
Furosemide	40
Bumetanide	1
Torsemide	20
Ethacrynic acid	50

IV = intravenous; PO = oral.

Patient Care Scenario

A 24-year-old woman with no pertinent medical history presents to the urgent care feeling very lightheaded and dizzy after having a stomach virus. Her blood pressure is 100/64 mm Hg. After laboratory tests are ordered, her Chem-7 is as follows: Na 137 mEq/L, bicarbonate 27 mg/dL, K 3.5 mEq/L, BUN 42 mg/dL, Cl 104 mEq/L, SCr 1.8 mg/dL, and glucose 180 mg/dL.

What is the most likely cause of this patient's AKI, and what treatment is best to recommend?

ANSWER

The patient has a prerenal AKI secondary to decreased perfusion to the kidney caused by the stomach virus that led to dehydration. The clinical evidence of a prerenal injury is that her BUN/SCr ratio is greater than 20:1, which is indicative of this type of AKI. Therefore, fluid resuscitation would be warranted in this patient.

1. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for the Acute Kidney Injury. Kidney Int Suppl 2012;2:1-138.
2. Palevsky PM, Liu KD, Brophy PD, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. Am J Kidney Dis 2013;61:649-72.

together with knowledge of specific drugs or drug classes (Bicalho 2015; Matzke 2008). Familiarity with drugs that have active or toxic metabolites is of utmost importance in using appropriate monitoring values as well as in following drug concentrations for identified narrow therapeutic index drugs. As the Vd of any drug increases, loading doses should be used to ensure the patient reaches a therapeutic concentration. Specifically, the hydrophilic antibiotic drug classes (β-lactams, cephalosporins, and carbapenems) have a significantly increased Vd in AKI, and increasing the loading dose up to 50% from what is typically recommended may lead to more appropriate initial dosing (Matzke 2011; Vilay 2008). Otherwise, clinical judgment should be used, especially knowing that nonrenal clearance can be improved in patients with an AKI. Medications should be initiated at doses that correspond with the patient's GFR and adjusted accordingly (Vilay 2008).

RENAL REPLACEMENT THERAPY

Renal replacement therapy may be warranted, either temporarily or chronically, if pharmacologic interventions do not resolve a patient's AKI. One of the main goals in patients with an AKI is to prevent the progression to CKD and to bring patients back to their baseline SCr. A process has been put into place to seek consensus and evidence-based recommendations regarding patients with AKI (Ronco 2001).

Use of RRT in a patient who has had an AKI is recommended when first-line strategies and interventions have been unsuccessful. Taking the vowel approach, "AEIOU" is a common way to evaluate a patient's need for RRT (Box 1-2).

Patients may need RRT in the acute setting because of acid-base abnormalities, electrolyte imbalances (most notably hyperkalemia), intoxications, fluid overload, and/or uremia. In patients with hyperkalemia, cardiovascular adverse effects can be modest to severe, including minor ECG changes to torsades de pointes; therefore, if pharmacologic therapy is ineffective at lowering potassium concentrations or if the patient is in cardiovascular distress, RRT is necessary. The need for RRT in patients with acute intoxications depends on the timing of the intoxication as well as whether the drug ingested is dialyzable. Common drugs that are dialyzable in an acute intoxication include lithium, salicylates, barbiturates, theophylline, methanol, and ethylene glycol. Specifically for fluid overloaded patients, RRT is indicated if they are diuretic resistant or for those with an emergency. Patients with uremia most commonly need RRT if they have CNS symptoms. The timing of RRT initiation can be very important with respect to why RRT was originally initiated, which is to prevent further renal insults; return to and maintain electrolyte, acid-base, and fluid balance; allow the ability to provide continued supportive care; and allow the kidneys to recover (KDIGO 2012). Early versus late initiation of RRT has been studied, but there is no consensus on the timing of initiating RRT, nor is there a reference definition (Ronco 2015). The longer delay in RRT initiation correlates with a higher mortality and longer lengths of hospital stay (Ronco 2015). There are obvious benefits of initiating RRT in patients who have an AKI together with an emergency need; however, RRT is not a lifelong commitment for these patients. The point at which RRT should be discontinued in a patient with a previous AKI should be discussed. As a patient's renal function begins to improve and the need for RRT no longer exists, withdrawal of RRT is indicated; however, this is not easily assessed, depending on the type of RRT the patient is receiving. Data suggest that if a patient requires RRT because of an AKI, the average treatment should last about 2 weeks (Ronco 2015).

Box 1-2. AEIOU Mnemonic for RRT

- A: Acid-base abnormalities
- E: Electrolyte abnormalities, especially evaluating for potassium imbalance
- I: Intoxications, specifically ingestion of a known dialyzable toxin
- O: Overload, either emergently fluid overloaded or diuretic resistant
- U: Uremia with neurologic symptoms

RRT = renal replacement therapy.

RRT Modalities and Components

When a patient needs RRT, the medical team must determine the most appropriate modality of dialysis to use, which will depend mainly on the patient's clinical status as well as the availability of the necessary resources at the institution for the different types of dialysis. Renal replacement therapy has greatly advanced over the past 40 years, and options for treatment modalities now range from intermittent hemodialysis (IHD), peritoneal dialysis, and CRRT to newer extended duration dialysis (EDD). Continuous renal replacement therapy includes continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF) (KDIGO 2012). Together with each dialysis modality, the clinician must evaluate the best parameters for the individual patient, including blood flow rate, solute transport, ultrafiltration rate, dialysate prescription, effluent volume, replacement fluid, and urea clearance. Of note, CRRT and EDD are used solely in the critically ill population. The dialysate includes purified water with electrolytes and other components specific to the patient's needs (Sam 2014). To describe solute transport in more detail, the importance of the dialysate and its components must be recognized, which is shown in Box 1-3. Unlike IHD, peritoneal dialysis dialysate does not contain potassium and uses lactate instead of bicarbonate.

Fluid is removed during dialysis by ultrafiltration. This occurs when fluid is transferred across a semipermeable membrane by a pressure gradient. This pressure gradient in IHD allows fluid to flow from high pressure, which is the blood, to low pressure, which is the dialysate. In peritoneal dialysis, the osmotic gradient leads to fluid transfer from low osmolarity, which is the blood, to high osmolarity, which is the dialysate.

Solute can be removed during dialysis by diffusion and/or convection. Removal by diffusion occurs when solute is transferred from areas of higher concentration to areas of lower concentration until equilibrium is reached. Removal of solute by convection occurs by pulling the solute across the membrane with the fluid during ultrafiltration. High-flux dialysis compared with conventional dialysis allows for shortened dialysis times and removal of larger molecules and higher fluid volumes. In addition, high-flux dialysis improves the overall efficiency of the dialysis process (Sam 2014). Published guidelines give no recommendations on which dialysis modality to choose secondary to the lack of the available literature and inconsistencies in the evidence for the critically ill population. What has come from the guidelines is based on patient-oriented information, specifically a patient's cardiovascular status. Intermittent hemodialysis is usually chosen in patients who are stable from a cardiovascular standpoint, whereas patients with hemodynamic instability or multiorgan failure typically receive CRRT or one of the newer "hybrid" therapies, such as EDD or sustained low-efficiency dialysis (SLED) (KDIGO 2012).

Box 1-3. Dialysate Components and Clinical Pearls for Intermittent Hemodialysis

Potassium

- Standard dialysate: Potassium 2 mEq/L
- After dialysis, potassium is typically low because of extracellular potassium removal from the blood
- An extracellular shift occurs in the hours postdialysis to create appropriate intracellular and extracellular potassium ratios
- Patients at risk of arrhythmias secondary to hypokalemia: Low predialysis potassium (in which case > 2 mEq/L could be added to the dialysate); on concomitant digoxin therapy

Chloride

- The primary anion accounted for in dialysate
- Higher chloride concentrations are incorporated in dialysate to ensure that electrical homeostasis is being maintained[a]

Glucose

- Standard dialysate: Dextrose 200 mg/dL
- Inclusion in dialysate is to decrease risk of hypoglycemia
- In hyperglycemia (> 200 mg/dL) before dialysis, the session will remove some glucose

Calcium

- Standard dialysate: Calcium 2.5 mEq/L
- Highly protein bound and therefore not easily dialyzed, which is why ionized calcium is part of dialysate
- Patients needing dialysis typically are hypocalcemic

Magnesium

- Standard dialysate: Magnesium 1.2 mg/dL
- Dialysis patients usually hypermagnesemic; therefore, goal is to remove magnesium
- No recommendation for magnesium dose in dialysate for a patient with hypomagnesemia

Bicarbonate

- Standard dialysate "base bath": ~35–40 mEq/L
- Added to maintain acid-base homeostasis, specifically metabolic acidosis that occurs in dialysis patients

[a]Gibbs-Donnan effect: when particles do not evenly distribute across a semipermeable membrane.

Information from: Sam R. Hemodialysis: diffusion and ultrafiltration. Austin J Nephrol Hypertens 2014;1:2010.

In the different RRT modalities, the choice of either IHD or CRRT does not affect patient survival rates; however, in the critically ill or hemodynamically unstable patient population, CRRT use is associated with a higher renal recovery rate than IHD use (Ronco 2015). The hybrid RRT modalities are a "meet-in-the-middle" approach between CRRT and IHD in which the IHD machines are used to provide longer dialysis sessions, recommended to be done 6–12 hours daily for up to 6–7 days a week, with decreased blood and dialysate flow

and efficiency (Wu 2010). Because of the decreased flows of blood and dialysate, patients can better tolerate the longer sessions, given the minimization of drastic osmotic shifts, providing patients with more hemodynamic stability. The trade-off is slower clearance of solutes and fluids; however, critically ill postsurgical patients with AKI receiving hybrid RRT have decreased ICU lengths of stay and 30-day mortality compared with patients receiving CRRT (Wu 2010).

Regarding drug dosing for patients receiving RRT, optimizing pharmacotherapy depends on the characteristics of the specific drug, including its molecular weight, protein binding, Vd, sieving coefficient, and unbound fraction, as well as the dialysis prescription. For further clarification, the sieving coefficient is defined as the amount of drug that can pass through a hemofilter, which is determined by unbound fraction of the drug and filter adsorption. Only unbound drug can pass freely through the filter; thus, as this amount increases, so does the sieving coefficient. In addition, the prescription for RRT, including the dialysis filter and surface area, patient's blood, dialysate, and ultrafiltration rate, is important in assessing the likelihood of the drug being dialyzed (Sam 2014). The clinical practice recommendations include giving drug doses after dialysis or, if the dosing regimen is not conducive to that, giving a supplemental dose after dialysis to make up for the fraction of drug that was removed (Lewington 2011). Moreover, it is recommended that supplemental doses be increased by 50% when patients undergo dialysis with high-flux synthetic dialyzers (Sam 2014). Patients with larger membranes who undergo dialysis with EDD have a much higher drug clearance; therefore, the supplemental dose of certain drugs may need to be increased. In patients receiving CRRT or EDD with a high effluent rate, clinicians should consider using higher doses than specified in the end-stage renal disease dosing recommendations, and because CRRT and EDD are continuous and extended sessions, respectively, the initial dose chosen for a particular medication may need to be adjusted over time according to the patient's renal function on CRRT or EDD. Specifically, CVVH has a higher degree of solute clearance than CVVHD if using a CRRT modality. Appropriate doses are optimally determined by obtaining drug concentrations for medications such as aminoglycosides, vancomycin, phenytoin, and digoxin; however, not much help is offered if medication concentrations cannot be obtained.

Renal Replacement Modalities

Intermittent Hemodialysis

Intermittent hemodialysis is the most commonly used type of RRT and has been in use since the 1940s. It is typically done three or four times per week for about 4 hours, or as long as the patient can tolerate the session. However, patients can have difficulty in tolerating IHD because of the significant fluid and solute shifts that can occur during a dialysis session in which volume status, electrolyte shifts, blood pressure control, and acid-base abnormalities may ensue. Intermittent hemodialysis is a single-pass modality with a moderate blood flow rate that runs countercurrent to the dialysate in order to filter necessary solutes and fluid. A contraindication to IHD is cerebral edema or increased intracranial pressure because the osmotic shifts associated with IHD can worsen or exacerbate the patient's condition. Caution must be taken when using IHD in patients who are hemodynamically unstable or who have multiorgan failure secondary to the difficulty of maintaining a steady and stable volume status. Advantages of IHD are its more rapid approach of removing toxins, solutes, or fluid in an emergency. Because IHD is not a continuous process, patients have time away from dialysis sessions for other testing and procedures. Membrane characteristics for IHD vary in permeability, and the blood flow rate and dialysate flow rate are greater than 200 mL/minute and greater than 500 mL/minute, respectively (KDIGO 2012).

Peritoneal Dialysis

Typically, peritoneal dialysis is not used for an AKI; however, in certain instances, it may be appropriate. These instances include hemodynamically unstable patients, difficult venous or arterial access, and a region that does not have extensive dialysis modality options secondary to limited resources (KDIGO 2012). Dialysate, typically containing glucose as the osmotic agent, is infused into the patient's peritoneal cavity and allowed to drain independently; however, there is a continuous equilibrium in which dialysate is infused into the patient's peritoneal cavity and is drained manually every 3–6 hours, with three or four cycles during the day and one long 8-to 10-hour cycle at night (KDIGO 2012). Advantages of using peritoneal dialysis include no need for anticoagulation or vascular access, lower cost than other modalities, and gradual and stable removal of toxins. However, the rate of fluid removal is not easily controllable; there is a risk of protein loss, hyperglycemia, peritonitis, and respiratory problems; and hypercatabolic patients have poor clearance of toxins when using peritoneal dialysis (KDIGO 2012).

Continuous Renal Replacement Therapy

Continuous renal replacement therapy is used for patients who are hemodynamically unstable or at risk of increased intracranial pressure. This modality allows for continuous, although slower, removal of toxins with a controlled way to manage fluid balance. Similar to IHD, fluid, acid-base, and electrolyte balance are maintained by dialysate and/or replacement fluid. However, patients receiving CRRT are exposed to anticoagulation for much longer periods, and the cost of initiating this modality is high. The membranes used in CRRT have a high permeability, and the blood flow rate and/or dialysate flow rate is less than 200 mL/minute and 17–34 mL/minute, respectively, depending on the modality used (KDIGO 2012). The CVVH process uses large-volume ultrafiltration and removes small- and middle-molecular-weight

molecules (500 Da to 60 kDa) by convection. Replacement fluid, with electrolyte concentrations similar to the desired blood concentration, is administered intravenously to replace the ultrafiltrate and maintain a patient's fluid status. The CVVHD process removes solute by diffusion as a dialysate is run countercurrent to blood flow. The CVVHDF process uses both diffusion and convection to remove solute and therefore requires both dialysate and replacement fluid (KDIGO 2012). Most replacement fluids and dialysate are commercially available with either lactate or bicarbonate as the base. The KDIGO guidelines recommend that the base of these fluids be bicarbonate secondary to its buffering ability and evidence that this choice can lower the risk of cardiovascular complications (Tian 2015). The ultimate goal in choosing the appropriate replacement fluid and dialysate is to maintain metabolic homeostasis during treatment.

Sustained Low-Efficiency Dialysis

The SLED process can also be called EDD and, as mentioned earlier, is considered a mix of IHD and CRRT. It is most commonly used when a patient is hemodynamically unstable. Because EDD is not continuous, the patient has more flexibility to undergo other procedures, tests, or diagnostics (Ronco 2015). Moreover, because the SLED modality is slower, the hemodynamically unstable patient benefits because of the slower clearance of toxins; therefore, emergency use is not appropriate for AKI. As mentioned previously, EDD can greatly affect medication dose optimization, which can in turn place the patient at risk of being underdosed, especially during the second half of the dialysis session (Ronco 2015).

Anticoagulation

Anticoagulant therapy is necessary in patients undergoing RRT as long as they have no contraindications to its use such as increased risk of bleeding or are already receiving systemic anticoagulation. Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) are the anticoagulants of choice in IHD. The dialysis circuit is typically rinsed with 5000–20,000 units of heparin before initiating IHD; subsequently, the recommended systemic dose of heparin is a bolus of 500–1000 units followed by 5–10 units/kg/hour. Maintaining the patient's activated prothrombin time (aPTT) at 30–45 seconds is the evidence-based recommendation (Sam 2014). Recommendations for using citrate anticoagulation in CRRT are graded higher than are those for UFH or LMWH unless a patient cannot tolerate or has a contraindication to citrate use (KDIGO 2012). Using citrate for CRRT binds calcium so that it cannot act as a cofactor in the clotting cascade (KDIGO 2012). Given this mechanism, the adverse effects of using citrate as an anticoagulant for CRRT include hypocalcemia, hypomagnesemia, and metabolic alkalosis. To restore adequate serum concentrations of calcium and magnesium, a patient's magnesium stores must be adequately replaced before initiating calcium replacement. Because of citrate's potential adverse effects, institutions have protocols that help guide the monitoring and adjusting of the citrate component. The extent of the deficiency, as well as the patient assessment, will determine whether these electrolytes should be replaced orally or intravenously as well as the recommended dose.

CONCLUSION

Acute kidney injury and dialysis are difficult topics for the clinician because patients have many different presentations, causes, disease states, and pharmacotherapy needs that guide the course of action. Establishing a patient's risk of developing an AKI is crucial because the main goal is to prevent an AKI from occurring. Focusing on high-risk patients in settings such as perioperative, contrast administration, and rhabdomyolysis presents additional opportunities to use preventive measures. Pharmacists must be able to identify the pharmacologic agents that can be increasing a patient's risk of an AKI, preventing resolution of an AKI, or requiring discontinuation. Treatment of a patient with an AKI, whether it be prerenal, intrinsic, or postrenal, should be initiated as soon as possible to meet the goals of returning a patient's renal function to baseline and avoiding the need for RRT. If RRT is required, understanding the pharmacokinetic and pharmacodynamic principles of drugs as well as the mechanisms of the different RRT modalities is critical in making appropriate decisions about medication therapy in this patient population.

Practice Points

Patients with AKI and those requiring dialysis are a critical population because early identification of the etiology and early intervention can prevent long-term implications.

- **As pharmacists, evaluating for drug causes of AKI, providing appropriate dosage recommendations, and recognizing nephrotoxic medications can prevent further insult as well as minimize any significant medication adverse effects.**
- **Recognizing patient risk factors for developing AKI is crucial, especially in the perioperative population, those receiving contrast media, and those initiated on drug therapy potentially associated with drug-induced kidney injury or disease.**
- **In a patient with an AKI, treatment depends on the etiology. In general, the underlying cause and patient-specific reason for a prerenal, intrinsic, or postrenal insult must be treated accordingly (e.g., fluid resuscitation for volume depletion in prerenal, discontinuation of aminoglycosides secondary to ATN, removal of obstruction in postrenal).**
- **RRT includes various modalities that have strengths and weaknesses in certain patient populations, as well as differences with respect to drug dosing concepts. Understanding the modalities and their effects on drug dosing can help the pharmacist provide appropriate recommendations for any modality, from the older to the newer RRT options.**

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Self-Assessment Questions

Questions 1–3 pertain to the following case.

L.J. is a 45-year-old woman seen in the clinic for complaints of blood in her urine. Her last visit was 2 weeks ago when she had acute sinusitis, for which she was prescribed amoxicillin/clavulanate 875 mg orally twice daily x 7 days. Her baseline SCr is 0.8 mg/dL; her SCr today is 1.7 mg/dL. L.J.'s medical history includes hypertension, hypothyroidism, and migraine headaches. Her home drugs include amlodipine 5 mg orally once daily, levothyroxine 100 mcg orally once daily, lisinopril 40 mg orally once daily, amitriptyline 25 mg orally at bedtime, and naproxen 500 mg orally every 12 hours as needed for headache.

1. Which one of the following best categorizes L.J.'s disease?

   A. Pseudo–drug-induced nephropathy
   B. Crystal nephropathy
   C. Acute allergic interstitial nephritis (AIN)
   D. Acute tubular necrosis (ATN)

2. Which one of the following drugs most likely contributed to L.J.'s diagnosis?

   A. Amoxicillin/clavulanate
   B. Lisinopril
   C. Amitriptyline
   D. Naproxen

3. Which one of the following is best to recommend for L.J.?

   A. Discontinue the offending medication.
   B. Do a renal biopsy, and initiate prednisone 60 mg orally daily for 10 days.
   C. Hold lisinopril and monitor the patient for improvement.
   D. Do nothing at this time.

Questions 4–6 pertain to the following case.

J.A. is a 78-year-old African American woman (height 61 inches, weight 50 kg) who is seen in the clinic today for a wellness screen. She complains of significant memory loss at times, and she feels as if "gravity is pulling her to the right." The physician orders CT of J.A.'s brain with and without contrast. Her medical history is significant for diabetes, congestive heart failure (CHF), hypertension, osteoarthritis, and herpes simplex virus. Laboratory values are as follows: Na 137 mEq/L, BUN 28 mg/dL, K 3.5 mEq/L, SCr 1.1 mg/dL, Cl 104 mmol/L, and CO_2 27 mmol/L. J.A.'s home drugs include aspirin 81 mg orally once daily, metformin 1000 mg orally twice daily, metoprolol succinate 100 mg orally once daily, lisinopril 20 mg orally once daily, furosemide 40 mg orally once daily, ibuprofen 400 mg orally three times daily, and acyclovir 400 mg orally twice daily.

4. Which one of the following is best to recommend for J.A. to prevent contrast-induced nephropathy (CIN)?

   A. Acetylcysteine 600 mg orally every 12 hours x 4 doses. The first two doses should be administered before contrast administration.
   B. Intravenous 0.9% normal saline at 1 mL/kg/hour 12 hours before and 12 hours after contrast administration.
   C. Sodium bicarbonate at 3 mL/kg/hour 1 hour before and 6 hours after contrast administration.
   D. Intravenous 0.9% normal saline at 1 mL/kg/hour as soon as possible before and 12 hours after contrast administration plus acetylcysteine 600 mg orally twice daily before and after contrast administration.

5. Which one of the following is best to recommend for J.A.?

   A. Continue all medications; monitor her renal function and urinary output after her CT for other medication adjustments.
   B. Hold metformin and lisinopril 24–48 hours before her CT; monitor her renal function and urinary output after her CT for other medication adjustments.
   C. Hold metformin, furosemide, ibuprofen, and acyclovir 24–48 hours before contrast; monitor her renal function and urinary output after her CT for other medication adjustments.
   D. Discontinue all drugs before contrast administration with the exception of preventive therapy in order to minimize any further risk of developing CIN.

6. Which one of the following best assesses J.A.'s receipt of iodinated contrast?

   A. The risk of developing CIN does not increase with higher dosages of iodine-based contrast dye.
   B. Iodine-based contrast dye is either ionic or nonionic; the ionic version leads to less risk of CIN.
   C. Many iso-osmolar contrast dye options are available and, although more expensive, are recommended in high-risk patients.
   D. Nonionic iso-osmolar contrast dye has not been shown superior to nonionic low-osmolar contrast dye with respect to preventing CIN in high-risk patients.

7. Which one of the following drug pairs would most likely significantly decrease a high-risk patient's intraglomerular pressure, possibly leading to acute kidney injury (AKI)?

   A. Gentamicin and allopurinol
   B. Benazepril and ketorolac
   C. Foscarnet and ceftaroline
   D. Lisinopril and sulindac

8. A 42-year-old woman presents to her primary care physician for a follow-up of a recent chronic obstructive pulmonary disease (COPD) exacerbation. The patient also has hypertension. Her home drugs include tiotropium 18 mcg 2 inhalations daily, albuterol metered dose inhaler 2 inhalations every 4–6 hours as needed, hydrochlorothiazide/triamterene 25/37.5 mg orally daily, and amlodipine 5 mg orally daily. The patient's blood pressure was 160/100 mm Hg at her last appointment and she was initiated on antihypertensive therapy. About 3 days ago she finished a 5-day course of azithromycin 500 mg orally daily and prednisone 40 mg orally daily. Laboratory records show that her SCr 3 months ago was 0.8 mg/dL; today it is 1.2 mg/dL. Her current blood pressure is 125/70 mm Hg. The patient has no complaints and states that she has been feeling "better than ever." Given this information, which one of the following is the most appropriate next step in this patient's treatment?

   A. Reorder a confirmatory SCr to determine whether a laboratory error occurred before taking any action.
   B. Hold triamterene, continue hydrochlorothiazide 25 mg, and reassess SCr within 2 weeks.
   C. Initiate normal saline 0.9% at 150 mL/hour and monitor her renal function and urinary output.
   D. No intervention is necessary because prednisone has already been discontinued.

9. An 82-year-old African American man (height 71 inches, weight 70 kg) was admitted to the ICU with a diagnosis of health care–associated pneumonia. His bronchoscopy cultures and susceptibility reports show multidrug-resistant *Pseudomonas* to all medications except tobramycin. His medical history includes chronic kidney disease (CKD), diabetes, hypertension, and COPD. Laboratory values are as follows: Na 134 mEq/L, BUN 38 mg/dL, K 4.1 mEq/L, SCr 2.2 mg/dL, Cl 101 mmol/L, glucose 220 mg/dL, and bicarbonate 27 mEq/L. The patient is at his baseline renal function. Which one of the following is best to recommend for this patient?

   A. Tobramycin 140 mg intravenously every 8 hours
   B. Tobramycin 490 mg intravenously daily
   C. Tobramycin 100 mg 1 inhalation every 12 hours
   D. Do not treat because it is colonization

Questions 10 and 11 pertain to the following case.

V.G. is a 45-year-old white man who was recently seen by his primary care physician. He was initiated on oseltamivir prophylaxis for influenza exposure and prednisone for an acute gout flare. One week later he has progressively worsened and presents to the ED. His blood pressure is 100/60 mm Hg and he has complaints of dizziness on standing, confusion, weakness, and nausea/vomiting. V.G. states that he has not noted how often he has been urinating. His medical history includes gout, anxiety, seasonal allergies, asthma, and fluid retention. His home drugs include allopurinol 100 mg orally once daily, lorazepam 1 mg orally twice daily as needed, cetirizine 10 mg orally once daily, albuterol 2 puffs every 4–6 hours as needed, and furosemide 40 mg orally twice daily. Laboratory values are as follows: Na 150 mEq/L, BUN 40 mg/dL, K 4.3 mEq/L, SCr 1.7 mg/dL, Cl 101 mmol/L, glucose 220 mg/dL, CO_2 28 mmol/L, and FENa 1.4%.

10. Which one of the following diagnostic criteria would be most helpful to the clinician to help diagnose a prerenal AKI?

    A. BUN/SCr ratio
    B. Fractional excretion of sodium
    C. Blood pressure
    D. All three.

11. Which one of the following drugs is most likely contributing to V.G.'s clinical presentation?

    A. Allopurinol
    B. Prednisone
    C. Cetirizine
    D. Oseltamivir

12. A 53-year-old woman was recently initiated on cisplatin 100 mg/m^2 every 4 weeks for metastatic ovarian cancer. She has received three treatments so far. Which one of the following pathophysiologic insults is best to monitor for in this patient?

    A. Crystal nephropathy
    B. Acute glomerulonephritis
    C. ATN
    D. AIN

13. A patient with an intrinsic AKI needs a pharmacologic intervention. Which one of the following is best to recommend for this patient if the physician wants to initiate therapy?

    A. Bumetanide intravenously 1 mg/hour
    B. Dopamine intravenously 2 mcg/kg/minute
    C. Fenoldopam 0.1 mcg/kg/minute
    D. Furosemide 80 mg orally x 1 dose

Questions 14 and 15 pertain to the following case.

N.G. is a 78-year-old African American woman who had an AKI secondary to her cyclosporine therapy, which was initiated 7 days ago after failed therapy for rheumatoid arthritis. Her AKI was found "by accident" when she presented to the ED with complaints of wheezing, pleuritic chest pain, and excessive sputum production. N.G. receives a diagnosis of pneumonia.

14. Which one of the following is best to recommend as the first-line intervention in managing N.G.'s AKI?

    A. Discontinue cyclosporine and initiate hydration.
    B. Continue cyclosporine and monitor concentrations because elevations in SCr are transient.

C. Discontinue cyclosporine and initiate fenoldopam.
D. Change cyclosporine to tacrolimus and monitor SCr and urinary output.

15. Which one of the following is most important to consider in recommending therapy for N.G.'s pneumonia?

A. No antibiotic should be initiated until her renal function returns to baseline or a new baseline is established.
B. Recognize that for an AKI, the Vd of hydrophilic antibiotics can be increased; therefore, a higher loading dose may be warranted.
C. Dosage adjustment of antibiotics is not necessary for an AKI because there are so many factors to consider; therefore, initiate therapy and monitor for adverse effects.
D. Wait for sputum culture and susceptibility reports so that the correct antibiotic can be chosen, thus limiting exposure to unnecessary therapy that may not be appropriate for an AKI.

Questions 16 and 17 pertain to the following case.

L.T., a 57-year-old African American man, is admitted to the hospital ICU secondary to acute decompensated heart failure (ADHF). His medical history includes type 1 diabetes, CHF, CKD, hypertension, and hyperlipidemia. His home drugs include aspirin 81 mg orally daily, furosemide 40 mg orally three times daily, spironolactone 100 mg orally twice daily, carvedilol 25 mg orally twice daily, insulin glargine 50 units subcutaneously twice daily, mealtime sliding scale with insulin aspart, lisinopril 40 mg orally daily, atorvastatin 80 mg orally at bedtime, and amlodipine 10 mg orally daily. L.T. receives a furosemide drip at 20 mg/hour and is producing minimal urine. The physician also notes crackles in the patient's lungs, increased work of breathing, and worsening peripheral edema. L.T. is noted to have a normal ECG but is considered hemodynamically unstable at this time. Laboratory values are as follows: Na 140 mEq/L, BUN 38 mg/dL, K 6.7 mEq/L, SCr 2.4 mg/dL, Cl 98 mmol/L, glucose 175 mg/dL, and CO_2 26 mmol/L.

16. Which one of the following is best to recommend for L.T.?

A. Give a dose of sodium polystyrene and increase the furosemide drip rate.
B. Recommend beginning continuous renal replacement therapy (CRRT).
C. Recommend intermittent hemodialysis (IHD).
D. Discontinue amlodipine.

17. L.T. is hemodynamically stable after appropriate treatment for ADHF, but he is still hyperkalemic and fluid overloaded. Which one of the following is best to recommend for L.T.?

A. Give a dose of sodium polystyrene, and increase the furosemide drip rate.
B. Recommend beginning CRRT or SLED.
C. Recommend that the patient undergo IHD.
D. Discontinue amlodipine because it is contributing to the patient's edema.

Questions 18–20 pertain to the following case.

J.J. is a critically ill woman (height 69 inches, weight 70 kg). She has been in the ICU for 5 days and has been receiving CVVH for 24 hours. On presentation, she had bacteremia. J.J. met the criteria for septic shock and was immediately initiated on vancomycin 1500 mg intravenously every 12 hours, piperacillin/tazobactam 4.5 g intravenously over 4 hours every 8 hours, and gentamicin 160 mg intravenously every 8 hours. Laboratory values are as follows: Na 132 mEq/L, Plt 350 billion/L, K 5.5 mEq/L, calcium 9 mg/dL, Cl 92 mmol/L, magnesium 2.3 mEq/L, CO_2 24 mmol/L, albumin 4 g/dL, BUN 47 mg/dL, SCr 3.7 mg/dL, and glucose 142 mg/dL.

18. Which one of the following is best to recommend for J.J.'s anticoagulation?

A. Initiate enoxaparin 70 mg subcutaneously every 12 hours.
B. Initiate heparin with a bolus of 500 units followed by 70 units/hour to target an aPTT of about 40 seconds, and monitor for thrombocytopenia.
C. Initiate argatroban 7 mcg/kg/minute.
D. Initiate citrate, and monitor for hypocalcemia, hypomagnesemia, and metabolic acidosis.

19. J.J. continues to receive CVVH. Which one of the following is the most important component of this process?

A. This modality uses convection to remove solutes and therefore requires an appropriate dialysate.
B. The patient needs replacement fluid with bicarbonate as the base secondary to decreased cardiovascular complications and its buffering ability.
C. Replacement fluid and dialysate for the patient should be chosen in order to maintain metabolic and electrolyte homeostasis.
D. Because the patient's presentation was emergent, the medical team should change her to EDD.

20. J.J.'s CRRT can be withdrawn. Which one of the following drugs is best to avoid as her renal recovery continues?

A. Vancomycin
B. Gentamicin
C. Piperacillin/tazobactam
D. Amphotericin B

Learner Chapter Evaluation: Acute Kidney Injury and Dialysis.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Given a patient's subjective and objective information, evaluate for the risk of an acute kidney injury (AKI).
13. Assess the appropriateness of using certain pharmacologic agents in patients at risk of developing an AKI.
14. Evaluate risk of AKI on the basis of subjective and objective patient information, and recommend appropriate preventive management.
15. Justify drug dosing changes and/or discontinuation in a patient with an AKI.
16. Distinguish the specific components and differences between hemodialysis, peritoneal dialysis, and continuous renal replacement therapy.
17. Evaluate the impact of each type of dialysis on medication dosing and recommendations.
18. Please provide any specific comments relating to any perceptions of bias, promotion, or advertisement of commercial products.
19. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Nephrolithiasis

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LEARNING OBJECTIVES

1. Distinguish the risk factors for developing nephrolithiasis.
2. Analyze acute treatment options for nephrolithiasis.
3. Assess dietary modifications to prevent recurrent nephrolithiasis.
4. Develop a pharmacologic treatment plan for preventing recurrent nephrolithiasis based on stone composition.

ABBREVIATIONS IN THIS CHAPTER

ESWL	Extracorporeal shock wave lithotripsy
MET	Medical expulsive therapy
RCT	Randomized controlled trial
URS	Ureteroscopic lithotripsy

Table of other common abbreviations.

INTRODUCTION

Nephrolithiasis, commonly known as kidney stones, is becoming increasingly prevalent in the United States. According to an analysis of the National Health and Nutrition Examination Survey (NHANES) 2007–2010 data, kidney stones were self-reported in 8.8% of the population (10.6% of men and 7.1% of women) (Scales 2012). These numbers have increased from previous NHANES II (1976–1980) and NHANES III (1988–1994) analyses, which had incidence rates of 3.8% and 5.2%, respectively (Stamatelou 2003). Although these surveys have shown higher rates of occurrence in men, the incidence appears to be increasing at a greater rate in women (Scales 2007). A medical history of nephrolithiasis can be an important finding because an estimated 39% of patients will have a symptomatic recurrence of a stone at 15 years (Rule 2014). This can lead to significant costs within the health care system, with an estimated 50% increase in the annual cost from 1994 to 2000 (Pearle 2005). Another study estimated the direct and indirect costs (e.g., loss of workdays) attributable to nephrolithiasis at $5.3 billion annually (Saigal 2005). Given the increasing prevalence and costs associated with nephrolithiasis, this chapter aims to educate pharmacists on using the best available evidence to recommend treatment options for patients with nephrolithiasis and to assist in preventing recurrence.

PATHOPHYSIOLOGY

Although the pathophysiology of nephrolithiasis has not been fully established, understanding the basic pathophysiologic process can facilitate comprehension of the mechanisms leading to stone formation and the rationale for specific treatment options and preventive therapies. Fundamentally, the formation of a stone results from an imbalance between solubility and precipitation of salts. Several factors, to be discussed later, can lead to the urine becoming supersaturated with insoluble materials. This can cause the formation of crystals that propagate and lead to the development of a kidney stone.

The specific pathogenesis of the kidney stone depends on the stone composition itself. The four main types of stone are calcium (oxalate and phosphate), uric acid, struvite, and cystine. The most common type of stone is calcium (consisting of about 80% of all stones), with most being calcium oxalate stones (Curhan 2015). Supersaturation of the urine increases the risk of calcium oxalate stone formation. Supersaturation can result from decreased urine volume, which can increase the risk of any type of stone. Alternatively, supersaturation can result from increased concentrations of urinary calcium (hypercalciuria), oxalate (hyperoxaluria), and/or uric acid (hyperuricosuria). Citrate can also play a role because it can form a complex with calcium to reduce to the availability of ionic calcium to bind phosphate or oxalate. In addition, the spontaneous precipitation of calcium oxalate can directly be inhibited by citrate. As a result, decreased citrate in the urine (hypocitraturia) can increase the risk of stone formation.

Regarding the other types of stones, acidic urine pH can lead to the formation of uric acid stones. Moreover, excessive amounts of uric acid in the urine can precipitate, as in patients undergoing chemotherapy resulting in tumor lysis (Davidson 2004). Struvite stones are commonly called "infection stones" because they are formed by chronic or recurrent infection of the genitourinary tract with urease-producing bacteria, which include *Proteus*, *Klebsiella*, and *Pseudomonas* (Curhan 2015). These bacteria metabolize urea to ammonia, which alkalinizes the urine and causes precipitation of calcium magnesium ammonium phosphate. Struvite stones may grow quite large, filling up the renal pelvis and calyces. Because of the shape of this enlarged stone, they are also known as staghorn calculi. Excess amounts of cystine excreted in the urine, seen with cystinuria, can lead to cystine stones. Stones typically develop in patients with the autosomal-recessive form of this genetic condition.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of signs, symptoms and diagnosis of nephrolithiasis
- Drug knowledge of agents used for medical expulsion therapy (e.g., tamsulosin, nifedipine) and recurrence (e.g., thiazides, allopurinol)

Table of common laboratory reference values

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- American Urological Association. Medical management of kidney stones: AUA guideline [homepage on the Internet].
- National Kidney Foundation. Kidney Stones [homepage on the Internet].

RISK FACTORS

Many factors can increase the risk of developing kidney stones (Box 2-1). Understanding the potential causes can influence treatment as well as guide prevention of recurrence and patient education interventions.

Dietary Considerations

Low urinary volume and high urinary concentrations of stone-forming solutes can increase a patient's risk of nephrolithiasis. Dietary factors, including fluid intake, can also affect a patient's risk. Of all dietary factors, fluid intake is likely the most important consideration because insufficient fluid intake leads to reduced urine volume and higher supersaturation. Choice of the right fluids for oral intake is also an important consideration because sugar-sweetened beverages can increase urinary excretion of calcium, and phosphoric acid–containing cola soft drinks can affect urine acidity.

Box 2-1. Risk Factors for Nephrolithiasis

Comorbid Medical Conditions

- Bariatric surgery
- Diabetes
- Gout
- Hyperparathyroidism
- Malabsorptive GI disorders
- Metabolic syndrome
- Obesity
- Renal tubular acidosis type 1
- UTIs

Drug-Induced Causes

- Acetazolamide
- Antiretrovirals (indinavir and atazanavir)
- Ciprofloxacin
- Loop diuretics
- Laxatives (abuse)
- Sulfonamides
- Topiramate
- Triamterene
- Vitamin C (> 1000 mg/day)

Dietary Intake Factors

- ↑ Animal protein
- ↓ Calcium
- ↓ Fiber
- ↓ Fluids (low urinary volume)
- ↓ Fruits and vegetables
- ↑ Sodium
- ↑ Sugar-sweetened beverages

Other Factors

- Family history
- Geography (Southern United States)
- Occupational (limited voiding)
- Temperature (warmer climate)

Furthermore, the risk of calcium stones can be considerably influenced by hyperoxaluria. It has been assumed that diets high in oxalate-containing foods (e.g., spinach, nuts) likely increase the risk of stones; however, studies with dietary intervention have not shown a strong correlation (Taylor 2008). Contrary to what one might think, increased calcium concentrations in the diet have no correlation with an increased risk of calcium stones. In fact, low dietary calcium intake may increase the risk. This is because dietary oxalate and calcium typically precipitate in the intestinal tract. This decreases the oral absorption of oxalate, which lowers urinary concentrations of oxalate. However, low calcium intake increases both intestinal oxalate absorption and urinary oxalate concentrations, which leads to a relative supersaturation of the urine. Greater intake of dietary fiber has been associated with a decreased risk of stones, which may be because fiber reduces the bioavailability of oxalate, resulting in decreased intestinal absorption (Sorensen 2014). Very high intake of ascorbic acid (vitamin C greater than 1000 mg/day) may also increase a patient's risk because ascorbic acid is a potential precursor of oxalate (Taylor 2004).

Other dietary factors that have been implicated as potentially increasing the risk of stone formation include increased animal protein intake, increased sodium intake, and decreased fruit and vegetable intake. Compared with vegetarian-based diets, diets high in animal protein have a higher prevalence of kidney stones. The acid load from the high-protein diet causes an acidic urine, which leads to an increase in urinary calcium and a decrease in urinary citrate. The metabolism of the proteins can also lead to a higher urinary oxalate and uric acid. Diets high in sodium intake can increase the risk of stone formation by causing hypercalciuria. Sodium excretion in the urine interferes with calcium reabsorption and proportionately increases the degree of hypercalciuria. The body can compensate by absorbing more calcium from the intestines and causing a thirst response, increasing fluid intake. Although the body can compensate if daily intake of sodium continually exceeds the recommended amount, the risk of stone formation becomes more of a concern. Similarly, diets low in fruit and vegetable intake are associated with hypocitraturia, which is associated with an increased risk of stones.

Comorbid Medical Conditions

Several comorbid conditions have been associated with nephrolithiasis. A cross-sectional analysis evaluated the number of metabolic syndrome traits (abdominal obesity, elevated blood pressure, impaired fasting glucose, increased TG, or decreased HDL) associated with self-reported kidney stones. The analysis showed that stone rates increased from 3% with zero traits to 7.5% with three traits and to 9.8% with all five traits of metabolic syndrome (West 2008). More specifically, looking at obesity and weight gain, one study evaluated three cohorts of patients: the Health Professionals Follow-up Study (45,988 men, baseline age 40–75 years), the Nurses' Health Study I (93,758 "older" women, baseline age 34–69 years), and the Nurses' Health Study II (101,877 "younger" women, baseline age 27–44 years) (Taylor 2005b). Those with a BMI of 30 kg/m^2 or greater were compared with those with a BMI of 21–22.9 kg/m^2. A higher BMI was associated with an increased risk of kidney stone formation in men (RR 1.33; 95% CI, 1.08–1.63), older women (RR 1.90; 95% CI, 1.61–2.25), and younger women (RR 2.09; 95% CI, 1.77–2.48). Similar results occurred when comparing a weight gain of greater than 15.9 kg (35 lb) since age 21 in men and since age 18 in women to the same age and gender group that did not gain weight. The authors concluded that both obesity and weight gain were risk factors for developing nephrolithiasis, with women more affected than men by these particular risk factors.

The same authors also evaluated the association between the prevalence of kidney stone formation and diabetes in a separate study. The relative risk of nephrolithiasis in individuals with diabetes compared with those without was 1.31 for men (95% CI, 1.11–1.54), 1.38 for older women (95% CI, 1.06–1.79), and 1.67 for younger women (95% CI, 1.28–2.20) (Taylor 2005a). Furthermore, a different cross-sectional analysis showed an increased risk of nephrolithiasis with both obesity and diabetes (Scales 2012). Compared with those of normal weight, patients with obesity had 1.55 times higher odds of self-reported kidney stones (OR 1.55; 95% CI, 1.25–1.94), with similar odds in those with a history of diabetes (OR 1.59; 95% CI, 1.22–2.07). By 2030, it is estimated that the increasing prevalence of obesity and diabetes with population growth will increase the cost of kidney stones by an additional $1.24 billion per year (Antonelli 2014).

From a pathophysiologic viewpoint, both obesity and diabetes decrease urinary pH, which makes uric acid less soluble in urine and contributes to an increased risk of uric acid stone formation (Daudon 2006). These individuals also excrete greater amounts of oxalate in their urine, which may predispose them to calcium oxalate stone formation (Eisner 2010; Taylor 2008). Similarly, patients with gout normally have acidic urinary pH, placing them at a higher risk of stone formation (Kramer 2002). Hyperoxaluria can occur after bariatric surgery and in malabsorptive GI disorders (Lieske 2015). Primary hyperparathyroidism can affect urinary calcium and phosphate concentrations and increase the risks of crystallization and stone formation (Vestergaard 2015). Other conditions associated with nephrolithiasis include renal tubular acidosis type 1 and UTIs caused by urease-producing bacteria. Although not a medical condition, excessive physical exercise (e.g., marathon running) can lead to crystalluria and increased risk of stone formation (Rodgers 1991).

Beyond dietary considerations and comorbid conditions, other risk factors of nephrolithiasis exist. One study showed that patients with a positive family history were more than twice as likely to develop kidney stones as were those with no family history (Curhan 1997). Geography and temperature may also factor into the risk of nephrolithiasis. Perspiration at

warmer temperatures can lead to increased urinary concentration of stone-forming solutes and their supersaturation. The Southern United States has been called the "stone belt" because of the higher rate of stones in these climates than in cooler states in the Northern United States (Soucie 1994). Similarly, concerns exist that global warming and excess heat exposure in urban areas will lead to an increased prevalence of stone formation (Goldfarb 2015; Brikowski 2008). In addition to environmental concerns, occupational exposures have been identified as an area needing further examination. Taxi drivers have an increased prevalence of kidney stones, which could be because of the routine suppression of the desire to void, leading to overdistension of the bladder and stone formation (Mass 2014). This also occurs in health care workers, as shown in a study of health professionals working in an operating room. Those who worked in the operating room had more stone formation (HR 1.43) and less fluid intake than non–operating room staff (Linder 2013).

Medication-Induced Causes of Nephrolithiasis

Various medications have been associated with an occurrence of kidney stones (see Box 2-1). The same risk factors for nephrolithiasis as previously described also place patients taking these medications at a greater risk of developing stones. Patients with a history of nephrolithiasis appear to be more susceptible to medication-induced calculi. In addition, drug-specific risk factors for medication-induced calculi exist. These include prolonged use of the drug, a high daily dose of the drug, low solubility of the drug or its metabolites, high urinary excretion of the drug or its metabolites, and short half-life of the drug, which could induce high urinary concentration peaks (Daudon 2004).

Medication-induced calculi are usually caused by one of two predominant mechanisms. The first mechanism relates to the medication's inducing a metabolic abnormality, which can occur with carbonic anhydrase inhibitors. These medications can block the resorption of sodium bicarbonate in the proximal tubule of the nephron, leading to a metabolic acidosis, which results in increased urinary pH and decreased urinary citrate. Because of the metabolic alteration, patients with prolonged use of topiramate or acetazolamide are at increased risk of developing calcium phosphate stones. Preventive measures include limiting sodium intake and increasing fluid intake (Rosenfeld 1997; Parikh 1994). Loop diuretics, which inhibit sodium and calcium absorption, can lead to a hypercalciuric state. Stones formed because of loop diuretics are composed of calcium oxalate. Laxative abuse can lead to excess ammonia in the urine and can form ammonium acid urate calculi in patients with hyperuricosuria. These stones can be mistaken for pure uric acid stones. Increased fluid intake and discontinuation of the laxatives should correct the metabolic abnormality (Dick 1990).

The second potential mechanism of medication-induced nephrolithiasis is caused by urinary supersaturation of the medication, leading to crystallization and stone formation. With this formation, the specific drug may be incorporated as a main component of the stone. Stones composed of specific drug components may be radiolucent on radiographic imaging. Proper identification is the most important aspect of managing these types of stones. Medications that could lead to stone formation include ciprofloxacin, sulfonamides, triamterene, and select antiretrovirals (e.g., indinavir and atazanavir) (Hamada 2012). Ciprofloxacin, sulfonamides, and antiretrovirals have a risk of crystallization with an alkaline urine pH. The mechanism for triamterene stone formation is unclear, but it is believed to occur because of precipitation of the medication or its metabolites, promoting stone growth. Patients presenting with stones caused by a medication should receive hydration and analgesics. The offending medication should at least temporarily be discontinued, and any metabolic abnormalities should be corrected. Seeking an alternative therapy option to the suspected medication is the best approach because drug discontinuation decreases the risk of recurrence.

Other than the specific agents mentioned earlier, antibiotic exposure overall has become an increased area of interest in relation to stone disease. This is because of the protective effect of the colonic bacterium *Oxalobacter formigenes*. Using oxalate as a source of energy, *O. formigenes* may metabolize oxalate in the intestine and reduce the amount available for absorption. It is hypothesized that a reduction in *O. formigenes*, which can occur with antibiotic use, can lead to an increased amount of available oxalate and, ultimately, increased urinary excretion of oxalate. One study found that 2 weeks of antibiotic treatment for a *Helicobacter pylori* infection had reduced colonization of *O. formigenes* at 1 month after treatment, which persisted at 6 months after treatment. Study authors proposed that this time interval would place a patient at risk of stone formation, and increased prescribing rates of antibiotics in the population could lead to a subsequent increase in stone prevalence (Kharlamb 2011).

ACUTE TREATMENT

Patients with nephrolithiasis may be asymptomatic or can present with a wide range of symptoms. Typically, patients present with hematuria as well as intermittent abdominal pain, flank pain, and cramping. This occurs because the stone travels within narrow portions of the urinary tract (i.e., ureter or urethra). As the stone travels in these narrow areas, the stretching stimulates pain receptors, leading to radiated pain. Renal colic, which is caused by a stone that has formed an acute obstruction, results in abrupt, severe flank pain and is often associated with nausea and vomiting. Finding a comfortable resting position can be difficult for patients with renal colic, and referral to an urgent care setting is needed.

Regardless of stone composition, all patients should receive an initial approach similar to acute management, including oral hydration and pain control. If patients cannot

take oral fluid, intravenous fluids should be used for hydration. There are no clear guidelines on pain management, but because of pain severity, prompt treatment is warranted. Use of NSAIDs by patients with acute renal colic has been evaluated in limited literature. The prostaglandin inhibition from NSAIDs is thought to reduce ureteric smooth muscle contractility and decrease local inflammation. However, NSAID use has not been shown to improve stone passage rates (Phillips 2009; Laerum 1995). A systematic review found that both opioids and NSAIDs provide clinically significant pain relief in acute renal colic. However, opioids were more likely to require rescue analgesia and had a higher incidence of vomiting (Holdgate 2005). A separate study comparing intravenous morphine with ketorolac found that the combination of the two provided better pain relief than either alone (Safdar 2006). In patients with opiate-seeking behaviors, an NSAID alone would be more appropriate. However, NSAIDs should be avoided in patients with renal dysfunction and should be discontinued before any anticipated procedures (e.g., extracorporeal shock wave lithotripsy [ESWL]) to minimize bleeding risk.

Beyond hydration and pain control, the stone size and probability of passage can help further guide the management strategy. A meta-analysis found that stones 5 mm or less have an estimated spontaneous passage rate of 68%. For stones between 5 mm and 10 mm, it was estimated that 47% would pass spontaneously. No spontaneous passage rates for stones greater than 10 mm were estimated in this meta-analysis, and these patients would most likely require surgical treatment options (Preminger 2007).

Diagnosis and Evaluation

Performing a detailed medical history, physical examination, and urinalysis will likely lead to a diagnosis of nephrolithiasis before radiographic confirmation. A helical CT scan is the gold standard for confirming diagnosis (Curhan 2015). Calcium stones are radio-opaque, but non-calcium stones may not appear on plain radiography. Even with a first stone occurrence, multiple stones revealed on initial imaging may likely represent recurrent disease. Serum chemistries should be measured, including uric acid and parathyroid hormone concentrations. Measurement of serum chemistries can help suggest associated conditions placing a patient at risk, such as elevated serum calcium and hyperparathyroidism or an elevated uric acid concentration and gout. If a stone is available, an analysis should be obtained. If there is no stone, patients should be instructed to strain their urine to capture any stones or fragments. The appearance of certain stone crystals may be pathognomonic for a type of stone composition. For example, struvite stones have "coffin-lid" crystals, and cystine stones have hexagonal crystals. The extent of evaluation needed for a first-time occurrence of a stone is controversial, but those with recurrent stones should have a more comprehensive analysis. This comprehensive analysis should include a 24-hour urine collection to measure total volume, pH, calcium, oxalate, uric acid, and citrate, though in practice, this evaluation is underused (Milose 2014). A low urine volume can result in increased urine concentrations and is a readily modifiable risk factor. Abnormal elevations in calcium (hypercalcuria), oxalate (hyperoxaluria), or uric acid (hyperuricosuria) can suggest potential risk, and particular stone composition can be used to help guide preventive treatment strategies. Similarly, low citrate concentrations (hypocitraturia) suggest an increased risk of stone formation because citrate is a natural inhibitor of stone formation. The optimal number of 24-hour urine collections is controversial; however, the American Urological Association suggests obtaining two measurements (Pearle 2014).

Surgical Procedures

If stones do not pass spontaneously, procedures such as ESWL, ureteroscopic lithotripsy (URS), and percutaneous nephrolithotomy can be considered. Advances in noninvasive surgical techniques have greatly improved the management of nephrolithiasis. A high-energy electrical pulse is created in ESWL, causing stone fragmentation, which helps facilitate stone clearance and resolution. The ESWL is a noninvasive procedure that can be performed under conscious sedation and has been successful. Some disadvantages of ESWL are that it may require several sessions for stone clearance and can cause short-term complications, including hematoma, tissue injury, posttreatment obstruction, and UTI.

The preferred procedure for large stones that are present in the kidney is ESWL. For stones in the ureter, or if an alternative to ESWL is needed, URS can be considered. A small scope is surgically placed in the bladder and ureter, allowing a surgeon to view the stone in the ureter and remove it. Some patients undergoing URS may need a stent placed to keep the ureter open to allow for stone removal. Potential complications include risk of infection, bleeding, or injury to the ureter. Large stones (greater than 2 cm) or those resistant to ESWL require percutaneous nephrolithotomy. Percutaneous nephrolithotomy is a surgical procedure in which the kidney is entered through a small incision to remove larger stones. As a minimally invasive surgery, potential complications include risk of infection, bleeding, and injury to nearby organs.

Medical Expulsive Therapy

For patients who are not candidates for or do not wish to undergo a surgical procedure, pharmacotherapeutic options have been used. Medical expulsive therapy (MET) refers to the use of pharmacotherapy to facilitate the passage of kidney stones. The American Urological Association recommends MET as an appropriate treatment option for patients who have stones less than 10 mm and reasonably controlled pain symptoms (Preminger 2007). The two most-studied drug classes for MET are dihydropyridine calcium channel blockers (predominantly nifedipine) and α_1-adrenergic receptor

antagonists (also known as *α*-blockers). Of the *α*-blockers, tamsulosin has been the most evaluated medication. Acting on the α-1D receptor that is predominant in the ureter and heavily present in the distal ureter, selective *α*-blockers (e.g., tamsulosin) have a theoretical advantage over nonselective *α*-blockers (e.g., terazosin, alfuzosin). This advantage can result in a reduced frequency and force of ureteral contraction (Sigala 2005). For the calcium channel blockers, nifedipine's clinical benefit can be explained by its ability to suppress smooth muscle contraction and decrease in vitro ureteral spasm (Davenport 2006). Corticosteroids have been evaluated as alternative treatment options for MET, but data are lacking, and they should not be routinely recommended (Dellabella 2005).

The American Urological Association and the European Association of Urology conducted a meta-analysis on stone passage rates with α-blockers and nifedipine as part of their 2007 guidelines for the management of ureteral calculi. Compared with control groups receiving placebo, groups receiving nifedipine had a 9% absolute increase in stone passage, but this difference was not significant (95% CI, –7% to 25%). In contrast, the analysis of groups taking *α*-blockers showed a significant increase in the stone passage rate of 29% (95% CI, 20%–37%) compared with control groups (Preminger 2007). However, although *α*-blocker use has had positive results in meta-analyses, more recent randomized controlled trials (RCTs) have had conflicting results. One study evaluated the efficacy of alfuzosin (n=34) compared with placebo (n=35) in facilitating the passage of distal ureteral calculi. Alfuzosin had no difference in stone passage rates after treatment compared with placebo (73.5% vs. 77.1%, respectively; p=0.83), but patients randomized to alfuzosin treatment had significant improvements in pain scores (p=0.0005) (Pedro 2008). To add further conflict regarding the use of *α*-blockers for MET, a separate study found passage rates of 77% with tamsulosin (n=61) and 70.5% with placebo (n=61) as well as mean stone passage times of 10.1 and 9.6 days, respectively (Vincendeau 2010). There was no statistical difference in stone expulsion after treatment with tamsulosin compared with placebo (p=0.41). Of note, these newer RCTs had higher stone passage rates than previous studies. In addition, the average stone of less than 5 mm can explain the difficulty in showing significant differences between MET and placebo.

Overall, most available trials have had small sample sizes or have lacked rigorous research design and methodology. This highlighted a need for further evaluation of MET and led to completion of the SUSPEND trial in 2015 (Pickard 2015). The SUSPEND trial, completed in the United Kingdom, was designed to determine the efficacy and cost-effectiveness of MET. The primary study outcome was spontaneous stone passage at 4 weeks. Patients were randomized to one of three groups: tamsulosin 0.4 mg orally daily, nifedipine 30 mg ER orally daily, or placebo. Of the 1136 patients included in the analysis, 80% in the placebo group passed their stone compared with 81% in the tamsulosin group and 80% in the nifedipine group. The OR for spontaneous stone passage with MET compared with placebo was 1.04 (95% CI, 0.77–1.43). For tamsulosin compared with nifedipine, the OR was 1.06 (95% CI, 0.74–1.53). No differences were found with respect to pain score, days of analgesic use, or time to stone passage. Because no significant difference was found with treatment, the planned cost-effectiveness analysis was uninformative. Overall, MET had no benefit compared with placebo. With respect to safety, patients were asked about study discontinuation on a 4-week questionnaire. Patient-reported discontinuation rates were 10% (25 of 247) for tamsulosin, 17% (40 of 241) for nifedipine, and 6% (15 of 231) for placebo. Given that this trial provides the best-quality evidence for evaluating MET at this time, there is reasonable concern regarding the validity of recommending MET. Future guidelines and recommendations will likely need to address these findings.

NONPHARMACOLOGIC PREVENTION OF STONE RECURRENCE

Stone recurrence exposes patients to many medical interventions and painful stimuli and simultaneously decreases quality of life. Earlier studies have estimated the risk of a second symptomatic stone occurring in a patient (i.e., recurrence) at 30%–50% within 5–10 years after the first event. Using medical records from the Rochester Epidemiology Project, a recurrence of kidney stone nomogram was developed (Rule 2014). The data used to create this nomogram had recurrence rates of 11%, 20%, 31%, and 39% at 2, 5, 10, and 15 years, respectively. Modifications in diet are the first and most important step in preventing recurrence. As much as possible, dietary modifications should be individualized to the specific patient and stone type. Pharmacists can play an important role in patient education, especially given that misinformation regarding dietary measures is readily available (Traver 2009).

Fluid Intake

A definitive threshold for urine volume and increased risk of stone formation has not been determined. However, because low urine volume can lead to increased urinary concentrations and play a large role in stone development, almost all patients should ensure adequate hydration. Although a universal recommendation for total fluid intake is not appropriate, given the intake of fluids found in foods and insensible losses, at least 2.5 L of urine output daily is an accepted goal (Pearle 2014). Ensuring proper urine output is thought to help prevent the formation of stones by decreasing urine stagnation and increasing urine dilution to limit supersaturation of stone components.

Limited-quality evidence is available to support specific fluid recommendations. Ideally, patients are maintaining their hydration with oral water intake. However, certain characteristics of water (specifically hardness) have been debated because of variability in mineral content. Evidence is unclear on whether hard water has a significant impact on

Table 2-1. Dietary Recommendations for Medical Management of Kidney Stones

Patient Population	Dietary Recommendations
All stone formers	Adequate fluid intake to ensure urine output ≥ 2.5 L/day
Calcium stone formers with hypercalciuria	Limit sodium intake and maintain normal calcium consumption (1000–1200 mg/day)
Calcium oxalate stone formers with hyperoxaluria	Limit intake of oxalate-rich foods and maintain normal calcium consumption
Calcium stone formers with hypocitraturia	Increase intake of fruits and vegetables and limit nondairy animal protein
Calcium or uric acid stone formers with hyperuricosuria	Limit intake of nondairy animal protein
Cystine stone formers	Limit sodium and nondairy animal protein intake

Information from: Pearle MS, Goldfarb DS, Assimos DG, et al. Medical management of kidney stones: AUA guideline. J Urol 2014;192:316-24.

kidney stone formation; this is likely the result of confounding factors in the various studies. These specifics may not be as important because patients may prefer to increase their fluid intake by consuming beverages other than water. Other beverages such as beer, coffee, orange juice, tea, and wine have all been associated with a decreased risk of stone formation. Patients should be instructed to avoid sugar-sweetened beverages (e.g., soda, punch) because they increase stone risk (Ferraro 2013). Fructose content is thought to be the reason for this risk because it can lead to increased urinary excretion of calcium, oxalate, and uric acid. Although orange juice contains fructose, it also contains potassium citrate, which provides favorable effects on the urine composition that are believed to outweigh the harm from fructose.

Dietary Recommendations

Even though dietary risk factors have been identified, evidence of dietary intervention aimed toward individual risks has not been studied or shown conclusive benefits. Similar to fluid intake, RCTs evaluating the efficacy of dietary recommendations in the treatment of nephrolithiasis are limited. In general, dietary studies have been of lower quality and have combined more than dietary measures (called a "multicomponent diet") to evaluate dietary intervention on the incidence of stone recurrence. This design limits the feasibility to determine whether one specific component of the dietary intervention is providing benefit or harm.

Because calcium stones are the most common stone type, most dietary intervention studies focus on patients with calcium stones. One study evaluated a multicomponent dietary intervention by randomizing men to one of two diets. The multicomponent diet consisted of normal dietary calcium intake, reduced animal proteins, and lowered sodium intake. This was compared with a diet low in dietary calcium. The multicomponent diet was superior to the low-calcium diet with respect to stone recurrence (20% vs. 38% recurrence rate at 5 years, respectively; p=0.04) (Borghi 2002). Although some may have initially thought that calcium should be restricted in those with calcium stones, this study added support to the contrary. Some evidence has suggested an increased stone risk with calcium supplementation compared with dietary calcium. However, this can be because of the timing of a calcium supplementation because taking it with meals can lead to a reduction in urinary oxalate.

A separate study randomized patients to three diets: high fiber, low animal protein, or usual/control diet. Compared with the control group, those placed on a high-fiber or low-animal-protein diet had no statistically significant difference in stone recurrence (Dussol 2008). Because of limited evidence, broad dietary recommendations for patients with a history of nephrolithiasis are not available. Taking into consideration pathophysiology and stone type, expert opinion and guideline recommendations provide options for patients most likely to benefit from certain dietary interventions (Table 2-1).

PHARMACOLOGIC PREVENTION OF RECURRENCE BASED ON STONE COMPOSITION

A challenge with recommending pharmacologic treatment options to prevent stone recurrence is the lack of quality evidence. There is a need in the literature for more insight on preventing recurrence with pharmacotherapy. All stone formers should receive dietary modifications as a first step and throughout their treatment plan. However, despite adherence to recommended dietary intervention, some patients will have recurring stones. These patients may require pharmacologic options to prevent stone recurrence. Knowing the specifics regarding initial stone type and urine abnormalities can be crucial in guiding further therapy to prevent future stones. Further text in this chapter will provide recommendations

Table 2-2. Pharmacologic Treatment Options to Prevent Recurrence

Stone Type and/or Urine Abnormality	Treatment Options	Monitoring
All stone formers	Dietary intervention (e.g., increased fluid intake)	Decreased stone recurrence, periodic 24-hr urine collection
Calcium		
Hypercalciuria	Thiazide (including thiazide-like) diuretics • Chlorthalidone (25–50 mg PO daily) • Hydrochlorothiazide (25 mg PO BID, 50 mg PO daily) • Indapamide (2.5 mg PO daily)	BMP, uric acid
Hypocitraturia	Potassium citrate 15–30 mEq PO BID	Serum potassium and creatinine
Hyperuricosuria	Allopurinol 200–300 mg PO daily	Serum liver enzymes
Uric acid	Potassium citrate 15–30 mEq PO BID (titrate to pH 6.0–6.5)	See above
Struvite	Acetohydroxamic acid (AHA) 250 mg PO BID–TID	CBC
Cystine	Tiopronin 800–1000 mg per day divided PO TID (titrate to pH 7.0–7.5)	CBC, BMP

BID = twice daily; BMP = basic metabolic panel; PO = oral(ly); TID = three times daily.

Information from: Pearle MS, Goldfarb DS, Assimos DG, et al. Medical management of kidney stones: AUA guideline. J Urol 2014;192:316-24.

on guiding pharmacologic treatment to prevent recurrence according to stone type and urine abnormality, which is also summarized in Table 2-2.

Calcium Stones

Hypercalciuria

Thiazide and thiazide-like diuretics are recommended to prevent recurring calcium stones in patients with hypercalciuria (Pearle 2014). Although most studies with thiazides evaluated patients with a history of calcium oxalate stones, some included those who developed calcium phosphate stones. Because a benefit occurred in both stone types, thiazide diuretic therapy is considered an appropriate treatment option for preventing all types of calcium stones in patients with hypercalciuria (Pearle 2014). Thiazides are an effective treatment option in hypercalciuria because the excretion of calcium into the urine is decreased by enhancing the renal absorption of calcium in the proximal and distal renal tubules. Chlorthalidone (25–50 mg orally daily), hydrochlorothiazide (25 mg orally twice daily, 50 mg orally daily), and indapamide (2.5 mg orally daily) have all been associated with significant hypocalciuric effects (Borghi 1993; Ettinger 1988; Laerum 1984). A review of five studies (316 patients) showed that patients treated with thiazide diuretics were 61% more likely to be stone free (RR 1.61; 95% CI, 1.33–1.96) (Escribano 2009). A reduction in sodium intake should be encouraged to maximize hypocalciuric effects and minimize potassium losses. To avoid potential thiazide-induced hypokalemia, potassium supplementation may need to be considered. Potassium citrate (discussed in the text that follows) may be a preferred replacement option because it can also benefit patients with hypocitraturia.

Despite data supporting higher doses of thiazide and thiazide-like diuretics to prevent stone recurrence, one study found that most patients are not treated with evidence-based dosing. Of those treated with hydrochlorothiazide (n=102), only 35% were treated with 50 mg orally daily. Hydrochlorothiazide 12.5 mg orally daily was prescribed to 13% of patients, and 25 mg orally daily was prescribed to 52% of patients (Vigen 2011). Prescribing doses lower than what has been shown to provide benefit in the literature can lead to subtherapeutic preventive therapy. This can be viewed incorrectly as a failed treatment option and may present an opportunity for pharmacists to intervene to improve efficacy.

Hypercalciuria is associated with decreased bone mineral density and increased bone resorption. Lower urinary calcium excretion with bisphosphonates can lead to their potential role in therapy (Giusti 2009). However, because no RCTs have specifically targeted stone recurrence with bisphosphonate therapy, this treatment option is not recommended at this time.

Hypocitraturia

Potassium citrate has a positive benefit on calcium oxalate stone recurrence (Ettinger 1997; Barcelo 1993). Citrate is an inhibitor of crystallization and may improve a low urinary pH.

Typical potassium citrate doses are 15–30 mEq orally twice daily. Aside from its potential for GI upset, it is generally well tolerated. Sodium citrate or sodium bicarbonate can also be used to treat hypocitraturia or low urinary pH as an alternative to potassium citrate. However, the relatively high sodium load from these agents can lead to increased urinary calcium excretion (Hofbauer 1994). In addition, urinary pH would need to be monitored to avoid overcorrecting and causing harm. If the pH exceeds 6.5, treatment should be withheld because of the risk of developing calcium phosphate supersaturation. As a result, potassium citrate is usually the preferred option, with the sodium-based options reserved for patients at risk of hyperkalemia. It has been proposed that citric acid beverages such as lemonade can be an alternative for increasing urinary citrate (Penniston 2007). However, lack of high-quality evidence prevents increased citric acid beverage intake as a routine treatment option.

Hyperoxaluria

Evidence regarding pharmacologic management of calcium stone formation caused by hyperoxaluria is limited. Consequently, dietary approaches remain the most important consideration for this patient population. Supplementation with magnesium and pyridoxine (vitamin B_6) has been an area of research in lowering urinary oxalate. Theoretically, magnesium forms a complex with oxalate to decrease the availability of calcium oxalate for stone formation. Noncontrolled trials have shown a benefit in stone recurrence rates with magnesium supplementation, but one RCT comparing magnesium with placebo showed no added value in stone recurrence (Ettinger 1988). Vitamin B_6 deficiency has been evaluated for a possible association with excess urinary oxalate, but no quality literature has supported the use of pyridoxine supplementation for prevention of stone recurrence. The previously discussed risk with *O. formigenes* has led to the hypothesis that giving the bacterium in the form of a probiotic can benefit those with hyperoxaluria. However, an RCT with oral *O. formigenes* showed no significant differences in urine oxalate concentrations compared with placebo when administered to patients with primary hyperoxaluria (Hoppe 2011). Use of *O. formigenes* remains an area of interest, with hope that it may be an effective probiotic for the treatment of hyperoxaluria in the presence of short bowel syndromes and inflammatory bowel disease.

Hyperuricosuria

Patients with recurrent calcium stones in the setting of hyperuricosuria can be treated with allopurinol, a xanthine oxidase inhibitor, to reduce the production of serum uric acid and subsequently decrease urinary uric acid load (Ettinger 1986). The urinary solubility of calcium is decreased with uric acid in the urine, and inhibiting xanthine oxidase to reduce uric acid production with allopurinol has had favorable results. Patients need not have hyperuricemia to benefit from xanthine oxidase inhibitor therapy. Allopurinol can be used with a usual dose of 200–300 mg orally per day in divided doses. Potential adverse effects include rash and liver abnormalities. Given its similarities, febuxostat has a potential role in preventing stone recurrence because it lowers urinary uric acid (Goldfarb 2013); however, it has not yet been shown to affect stone recurrence. Therefore, further clinical research on the preventive effects of febuxostat is needed before it can be recommended as an alternative to allopurinol.

Uric Acid Stones

Contrary to what may be a common perception, low urinary pH rather than hyperuricosuria is the main contributor to uric acid stone development (Maalouf 2004). Therefore, it is recommended that allopurinol be avoided as a routine first-line therapy option for patients with uric acid stones. The primary treatment option for patients presenting with uric acid stones is urinary alkalinization. As discussed with calcium stones, potassium citrate can be used to achieve this alkalinization. In this setting, urinary pH may need to be monitored to achieve a goal range of 6.0–6.5 for the best outcomes. If urinary alkalinization alone is unsuccessful, allopurinol can be considered as adjunctive therapy.

Struvite Stones

Surgical treatment is often necessary for struvite stones. Systemic antibiotic therapy can be provided and should be guided by urine cultures. Because sterilizing the urine with antibiotic therapy can be difficult if bacteria are colonized on the stones, surgery is usually the appropriate option for these patients. Acetohydroxamic acid has been evaluated as a potential agent for prevention for patients unable to undergo a surgical procedure. The medication blocks urease and prevents the hydrolysis of urea and ammonia production in the urine, which is needed for struvite stone formation. As surgical procedures continue to improve, the future role of acetohydroxamic acid in struvite stone management is unclear. The starting dose of acetohydroxamic acid is 250 mg orally twice daily, which can be titrated to three times daily in about 1 month, if well tolerated. Significant adverse effects such as pulmonary embolism, deep venous thrombosis, headache, and tremor have been reported with acetohydroxamic acid use. This adverse effect profile may further limit the continued use of acetohydroxamic acid (Griffith 1991).

Cystine Stones

Cystinuria, a genetic disorder causing defective resorption of filtered dibasic amino acids, leads to excessive urinary excretion of cystine and is the common cause of cystine stones. These are the least common stone type, and great advances in treatment have not occurred. First-line therapy consists of urinary alkalinization, increased fluid intake, and restriction of sodium and protein intake. If these measures are unsuccessful in preventing stone recurrence, a cystine-binding thiol drug should be used (Pearle 2014).

Patient Care Scenario

A 43-year-old woman (weight 75 kg) is in your clinic for a routine follow-up. She states that she went to the ED over the weekend for severe pain, where she was given a diagnosis of a kidney stone. This is her third stone in the past 2 years. She does not appear to have any extensive documentation in her medical record regarding her history of nephrolithiasis. Her medical history includes type 2 diabetes and hypertension. Current medications are metformin 500 mg orally twice daily and lisinopril 20 mg orally daily. Her BMI is 30.2 kg/m^2, blood pressure 148/98 mm Hg, and most recent A1C 8.0%.

The patient asks if she can take a medication to help prevent another kidney stone. What would be the best recommendation for this patient?

ANSWER

The best options for this patient at this time are to encourage improved control of modifiable risk factors, further laboratory testing, and dietary changes. Both the patient's obesity and her diabetes can place her at a greater risk of developing kidney stones. This risk can be decreased with better control of these factors. A more detailed history of her dietary habits should be obtained to identify any dietary risk factors. The patient has a 24-hour urine collection to identify any abnormalities that might guide specific dietary interventions or further therapeutic recommendations. For example, if she is found to have hypercalciuria, adding a thiazide can be considered to decrease urinary excretion of calcium while providing improved blood pressure control. The urine collection can provide insight on urine volume, but the patient can also be instructed to increase fluid intake at today's visit without waiting for the test results.

1. Pearle MS, Goldfarb DS, Assimos DG, et al. Medical management of kidney stones: AUA guideline. J Urol 2014;192:316-24.
2. Escribano J, Balaguer A, Pagone F, et al. Pharmacological interventions for preventing complications in idiopathic hypercalciuria. Cochrane Database Syst Rev 2009;1:CD004754.

Pharmacotherapy treatment options for patients with cystine stones include thiol-containing drugs, d-penicillamine, and tiopronin (α-mercapto propionylglycine). Tiopronin undergoes a thiol-disulfide exchange with cystine to form tiopronin-cystine disulfide, which is more soluble than cystine. Similarly, penicillamine also binds with cystine to form a more readily dissolvable disulfide. Although no quality RCTs support the use of these agents, limited evidence shows decreased rates of stone formation with these treatments for patients whose first-line treatment options have failed (Chow 1996). Both drugs are considered equally effective and have a similar safety profile, but penicillamine has more serious and common hematologic, hepatic, and renal adverse events than tiopronin. Because tiopronin appears to be better tolerated, it is the preferred option in this class. Typical dosing is 800–1000 mg orally in three divided doses, with common adverse effects including rash, arthralgia, and fever. The dose should be adjusted to reduce the cystine concentration to below the solubility limit (generally less than 250 mg/dL). Captopril, which contains a thiol group, was evaluated as a theoretical treatment option for patients with cystinuria. However, its ability to reduce urinary cystine has not been supported in the available literature (Michelakakis 1993).

Practice Points

- **Knowing risk factors for nephrolithiasis can not only help identify patients at high risk, but can also lead to modifiable areas to prevent recurrence of nephrolithiasis.**
- **Stones composed of specific drug components may be radiolucent and not appear on radiographic imaging.**
- **Evidence appears to be insufficient to routinely recommend pharmacotherapy for MET.**
- **Increased fluid intake is likely the most important dietary recommendation.**
- **Thiazide and thiazide-like diuretics and potassium citrate have the best evidence for options to prevent the recurrence of calcium stones.**
- **Allopurinol is a good option in the setting of calcium stones and hyperuricosuria. However, alkalinizing urinary pH, not allopurinol, is a better option for uric acid stones.**
- **Overall, high-quality evidence for pharmacologic prevention of recurrence is limited.**

CONCLUSION

The prevalence of nephrolithiasis is increasing, likely influenced by a similar increase in identified risk factors such as diabetes and obesity. High-quality evidence is limited, so pharmacists must use the best information available to provide treatment recommendations. Dietary modifications can play a key role in preventing stone recurrence. Proper patient education and encouragement can be an important role for pharmacists. If stones recur despite dietary interventions, further pharmacotherapy options for prevention exist. Selection of appropriate medications should be dictated by stone type and urine abnormalities. Ultimately, pharmacists can have a vital impact on treatment success.

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Self-Assessment Questions

Questions 21–24 pertain to the following case.

T.Z., a 40-year-old accountant with a history of recurrent kidney stones, presents to your clinic for future treatment considerations. He is prescribed colchicine 0.6 mg orally as needed because of his medical history of gout. His current drugs also include nifedipine ER 30 mg orally daily, which was prescribed 6 months ago after he presented to the ED with a kidney stone. When asked about any recent changes in his diet, T.Z. states that he has been drinking more hot tea lately because of the cold weather. Before this follow-up visit, he was able to collect a stone fragment by straining urine; he also completed a 24-hour urine collection. Analysis reveals a calcium oxalate stone and hypercalciuria. T.Z. wishes to start treatment to prevent further stone recurrence.

21. Which one of the following factors best represents T.Z.'s greatest risk factor for recurrent nephrolithiasis?

    A. Climate
    B. Medication
    C. Medical history
    D. Occupation

22. Which one of the following dietary interventions would be best to recommend for T.Z.?

    A. Increase fluid intake and decrease sodium intake.
    B. Increase calcium intake and decrease fiber intake.
    C. Increase fluid intake and decrease calcium intake.
    D. Decrease sodium intake and decrease fiber intake.

23. Which one of the following is best to recommend for T.Z. regarding treatment with nifedipine?

    A. Change to tamsulosin.
    B. Continue nifedipine.
    C. Discontinue nifedipine.
    D. Double the nifedipine dose.

24. Which one of the following would be best to recommend to prevent recurrent kidney stones in T.Z.?

    A. Allopurinol
    B. Febuxostat
    C. Hydrochlorothiazide
    D. Potassium citrate

25. A physician requests a pharmacotherapy consult to provide a medication review for a patient with nephrolithiasis because it is suspected the stone is made of a medication component based on preliminary analysis. Assuming the patient is taking all of the following medications, which one would be the most likely cause?

    A. Triamterene
    B. Furosemide
    C. Topiramate
    D. Cephalexin

26. A primary care physician asks about using tamsulosin for medical expulsive therapy (MET). Which one of the following descriptions of the SUSPEND trial is the best to provide to this physician?

    A. No clear benefit of tamsulosin in MET has been established.
    B. Tamsulosin was superior to nifedipine for MET.
    C. Tamsulosin improves pain scores when used for MET.
    D. Time to stone passage is improved with tamsulosin.

27. A patient has recurrent calcium oxalate stones; the 24-hour urine collection shows that the patient has elevated urinary uric acid concentrations. Which one of the following would best prevent recurrent stones in this patient?

    A. Allopurinol
    B. Febuxostat
    C. Hydrochlorothiazide
    D. Potassium citrate

Questions 28 and 29 pertain to the following case.

M.B., a 48-year-old woman with a history of nephrolithiasis, is being followed as an outpatient to prevent recurrent stones. A previous stone analysis indicated uric acid stones, and a recent 24-hour urine collection showed a low urinary pH.

28. Which one of the following drugs, if initiated, would best decrease M.B.'s risk of a future stone?

    A. Allopurinol
    B. Febuxostat
    C. Hydrochlorothiazide
    D. Potassium citrate

29. Which one of the following is the best treatment goal for M.B.?

    A. Urinary pH 6.0–6.5
    B. Serum uric acid less than 6 mg/dL
    C. Urinary calcium less than 300 mg/day
    D. Urine output greater than 3.5 L/day

30. A patient recently treated with atazanavir 400 mg orally daily developed a kidney stone, and the new medication is the suspected cause. Which one of the following is the most likely mechanism for this patient's stone development?

    A. Induction of a metabolic alkalosis
    B. Crystallization with an alkaline urinary pH
    C. Inhibition of urinary calcium absorption
    D. Reduction of *O. formigenes* in the colon

Question 31 and 32 pertain to the following case.

J.M. is a 45-year-old woman who presents to urgent care with hematuria and abdominal and flank pain. She is having difficulty finding a comfortable resting position. On initial evaluation, J.M. is thought to have a kidney stone.

31. Which one of the following is the best initial approach to recommend for J.M.?

    A. CT to confirm diagnosis
    B. Intravenous fluids and pain management
    C. Oral fluids and 24-hour urine collection
    D. Referral for surgical evaluation

32. It is determined that J.M. has a 15-mm stone in her kidney. Which one of the following is best to recommend for J.M.?

    A. Allow the stone to pass spontaneously.
    B. Consider ureteroscopic lithotripsy (URS).
    C. Refer for to surgery for percutaneous nephrolithotomy.
    D. Undergo extracorporeal shock wave lithotripsy (ESWL).

Questions 33 and 34 pertain to the following case.

R.T. is a 62-year-old man evaluated for nephrolithiasis after a first occurrence of a kidney stone. He has no significant medical history other than a recent UTI. An initial examination of R.T.'s stone reveals "coffin-lid" crystals.

33. Which one of the following best describes the type of kidney stone R.T. passed?

    A. Calcium phosphate
    B. Cystine
    C. Struvite
    D. Uric acid

34. Which one of the following is best to recommend for R.T.?

    A. Antibiotic therapy
    B. Dietary intervention
    C. Thiazide diuretic
    D. Urinary alkalinization

35. A patient with a history of cystinuria is evaluated for recurrent nephrolithiasis. She has never received interventions to prevent recurrence. Which one of the following is best to recommend first for this patient?

    A. Antibiotic therapy
    B. Increased fluid intake
    C. Penicillamine
    D. Tiopronin

36. Serum chemistries and a 24-hour urine collection are ordered for a patient with recurrent nephrolithiasis. Which one of the following abnormalities would place this patient at greatest risk of stone formation?

    A. Hypercalcemia
    B. Hyperuricemia
    C. Hypocitraturia
    D. Increased urinary volume

Questions 37 and 38 pertain to the following case.

V.K. is a 58-year-old man who comes to the clinic for a follow-up. He was recently in the ED for a second occurrence of kidney stone. A further evaluation revealed that V.K. had passed a uric acid stone, but he has not yet received any intervention to prevent recurrence. His medical history includes diabetes, hyperlipidemia, hypertension, and primary hyperparathyroidism.

37. Which comorbid conditions is most likely to increase V.K.'s risk for this type of stone formation?

    A. Diabetes
    B. Hyperlipidemia
    C. Hypertension
    D. Primary hyperparathyroidism

38. The stone V.K. passed was found to be calcium oxalate. Which one of the following is the best dietary recommendation for V.K.?

    A. Avoid sugar-sweetened beverages.
    B. Eliminate oxalate consumption.
    C. Limit calcium intake.
    D. Increase fiber intake.

39. The primary care physician for a patient with recurrent nephrolithiasis consults with the pharmacist regarding dietary recommendations for preventing stone recurrence. Which one of the following is the best information to provide this physician?

    A. Non–cola-based soft drinks are associated with an increased risk of stone formation.
    B. The amount of fluid intake is more important than urine output.
    C. Definitive evidence exists for many known dietary risk factors.
    D. Many dietary studies have combined multiple interventions.

40. A patient with a history of nephrolithiasis recently had another kidney stone. The patient states that he has been adherent to hydrochlorothiazide 25 mg orally daily, which was initiated after evidence of a calcium oxalate stone. A 24-hour urine collection has not yet been completed, but serum chemistries for today's visit show Na 140 mEq/L, K 2.9 mEq/L, Cl 100 mmol/L, BUN 16 mg/dL, CO_2 22 mmol/L, SCr 1.0 mg/dL, and glucose 98 mg/dL. Which one of the following is best to recommend for this patient?

    A. Add potassium citrate 15 mEq orally twice daily.
    B. Change hydrochlorothiazide to chlorthalidone.
    C. Continue current treatment.
    D. Increase hydrochlorothiazide to 50 mg orally daily.

Learner Chapter Evaluation: Nephrolithiasis

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

20. The content of the chapter met my educational needs.
21. The content of the chapter satisfied my expectations.
22. The author presented the chapter content effectively.
23. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
24. The content of the chapter was objective and balanced.
25. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
26. The content of the chapter was useful to me.
27. The teaching and learning methods used in the chapter were effective.
28. The active learning methods used in the chapter were effective.
29. The learning assessment activities used in the chapter were effective.
30. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

31. Distinguish the risk factors for developing nephrolithiasis.
32. Analyze acute treatment options for nephrolithiasis.
33. Assess dietary modifications to prevent recurrent nephrolithiasis.
34. Develop a pharmacologic treatment plan for preventing recurrent nephrolithiasis based on stone composition.
35. Please provide any specific comments relating to any perceptions of bias, promotion, or advertisement of commercial products.
36. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter.

Biostatistics and Study Design

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LEARNING OBJECTIVES

1. Apply various types of data to interpret study results.
2. Evaluate clinical trial design with respect to relevancy of end points, effect size, and sample size, as well as interpretation of noninferiority and equivalence trials.
3. Distinguish the role of bias in designing, conducting, and analyzing clinical trials.
4. Interpret the use of systematic review, meta-analysis, and adaptive design in clinical trials.
5. Analyze the role of comparative effectiveness research in regulatory approval and clinical interpretation.

ABBREVIATIONS IN THIS CHAPTER

AHRQ	Agency for Healthcare Research and Quality
AMSTAR	Assessment of multiple systematic reviews
ARRA	American Recovery and Reinvestment Act of 2009
CER	Comparative effectiveness research
EHC	Effective Health Care (AHRQ program)

Table of other common abbreviations.

INTRODUCTION

A pharmacist's ability to interpret data from clinical trials is a vital skill in the modern interprofessional practice setting. This chapter will provide updates for the clinician on advances in clinical trial design and interpretation, as well as a context for applying the essentials of data classification and analysis to components of study design.

FUNDAMENTALS OF DATA ANALYSIS

Data are mainly classified as discrete or continuous. Discrete data can then be classified further as either nominal or ordinal. Similarly, continuous data can be further classified as either interval or ratio. Figure 3-1 shows the classification of data and examples of each type.

Descriptive Statistics

Descriptive statistics are used to characterize data without doing hypothesis testing. Descriptive statistics can report summaries through different means such as number, percent, range, standard deviation (SD), and so forth and are the foundation to analyzing data.

Measures of Central Tendency

Among the many ways to define the central tendency of a data set are mean, median, and mode. Although these are similar in normally distributed data sets, outliers can affect the interpretation of non-normal data sets, and the mean is an inappropriate measure of discrete data types. Choice of the appropriate measure of

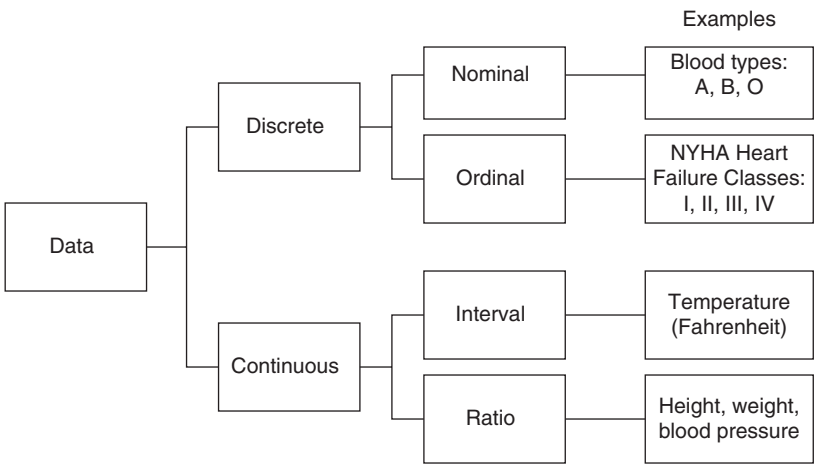


Figure 3-1. Basic data classification scheme.

NYHA = New York Heart Association.

central tendency depends on the type and distribution of the data under evaluation. Table 3-1 describes when each measure of central tendency is used.

Measures of Dispersion

Dispersion is a measure of how spread out the values in a data set are from one another. Combining central tendency and dispersion provides a more substantive image of what the data represent.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the purpose of data collection and analysis.
- Basic understanding of the scientific method and associated terminology.
- Role of governmental organizations (e.g., the FDA) in drug approval.

Table of common laboratory reference values

ADDITIONAL READINGS

The following resources have additional background information on this topic:

- FDA. Center for Drug Evaluation and Research (CDER) [homepage on the Internet].
- GraphPad Statistics Guide [homepage on the Internet].
- Altman DG. Bland JM. Statistics notes series. 1994-present [homepage on the Internet].

The simplest evaluation of dispersion is range, calculated by subtracting the smallest from the largest value. Percentile provides a better assessment of the distribution of values than the range and represents the point at which a given value is larger than the percentage of the other values within a data set. For example, the 80th percentile of a data set represents the point at which 80% of the other values in that set are smaller. The interquartile range represents the difference between the 25th and 75th percentiles. It is useful as a measure of dispersion when the data set has a non-normal (i.e., skewed) distribution and is best paired with median as a measure of central tendency.

For continuous data, the SD of a data set represents the specific index of variability of data around the mean of those data. Standard deviation is generally used when the data can be expected to have a normal distribution and is paired with mean as a measure of central tendency.

Sample size (n) is directly related to another measurement of dispersion, known as the standard error of the mean (SEM). Also called the "standard deviation of the mean," the SEM estimates the variability of a sampling distribution mathematically and is calculated by dividing the SD of a sample by the sample size (SEM = SD/√n). Because the sample size is on the denominator of this calculation, it is inversely related to the SEM – as the sample size increases, the SEM decreases.

The SEM is directly related to another familiar measurement – the 95% confidence interval (95% CI). The 95% CI includes the values that are 1.96 times the SEM above and below the mean. In practice, the 95% CI is a range of values that we can be 95% sure to contain the true mean of the population. A wide CI indicates uncertainty regarding where the true population mean lies, whereas a narrow CI indicates relative certainty regarding the population mean.

Table 3-1. Classifying and Analyzing Data

Measure of Central Tendency	Appropriate Data Type(s)	Sensitivity to Outliers	Method to Determine
Mean	Normally distributed continuous data sets	Yes	Sum of observations/No. of observations
Median	Asymmetrical continuous data sets Ordinal data sets	No	Middle value within ordered data sets
Mode	Nominal data sets Ordinal data sets	No	Most commonly occurring data point

Inferential Statistics

Hypothesis Testing

A hypothesis is a declarative statement that examines or summarizes the relationship between groups. Following the scientific method, study designers must first assume that what they are trying to prove is false and then use a test to "prove" that any difference found is because of a real difference present, not simply because of chance alone. The null hypothesis (H_0) is usually stated as no difference between the variables in question. In contrast, the alternative hypothesis (H_A) is what the study designers are trying to prove with their investigation. This methodology places the burden on the study investigators to prove that the H_A is true and assumes first that the H_0 (the opposite of the H_A) is true.

Sampling Strategies

In some circumstances, true random sampling may not be possible or even desired, depending on the goals of the study. A convenience sample, named after the nature of the collection process, is gathered by researchers according to specific circumstances or around specific times or locations. Another sampling methodology involves choosing members of the population to include in the sample in a systematic manner ("systematic" or "systematic random" sampling). This method is less robust than a fully randomized sample, but it applies a type of logic to the selection process. With systematic sampling, the study designer chooses subjects in a regular, predictable manner, such as every 15th patient seen at a clinic; however, the sample is not truly random because many unforeseen factors can affect the order of patients seen and potentially bias the results.

When true random sampling is impossible or not desired, such as when members of the population with certain characteristics are needed (e.g., people older than 50, women age 18–35), researchers may use stratified sampling. Because the key characteristic of the strata is often part of the analysis (e.g., an age-related illness for people older than 50), these strata should not overlap with each other and should have similar parameters to ensure internal validity. Within these strata, designers may use any type of sampling, according to the study design.

ELEMENTS OF CLINICAL TRIAL DESIGN

In general, clinicians look to randomized controlled trials for the most robust evidence and the most solid justification for treatment decisions (Pocock 2015). Randomized controlled trials are part of the evidence package submitted by sponsors to the FDA when a drug, treatment, or, more recently, medical device is up for approval in the United States.

Chief Components of Designing Clinical Trials

Critical to a trial is the existence of a relevant clinical question. In addition, several key factors are fundamental to proper trial design: patient selection, appropriate treatment(s), identification of key outcomes, and blinding (Pocock 2015; Chan 2013). Although these aspects may not apply to all trials and are not always completed in that order, they represent the basic tenets of what researchers should consider.

During the planning phase of a study, researchers consider which type(s) of patients should be selected for inclusion in the study. Some trials focus on conditions that only occur in a select group of the population, so the types of patients included in these trials are limited by that population itself. In such trials, the demographics of the population selected should reflect the broadest possible population to increase the applicability of the study results.

The treatments chosen for the various groups of patients in a study (i.e., "study arms") are also a key component in trial design. In studies evaluating new treatments, one of the groups receives the treatment or device being evaluated; however, investigators must still choose whether any comparator group(s) will receive placebo, active treatment, or some combination. No specific requirement exists for sponsors to include existing treatments in comparator groups, outside the conditions in which ethics dictate a treatment being given (e.g., salvage chemotherapy, conditions with well-accepted guidelines for treatment).

Another important aspect of trial design is determining the outcomes that will be measured and compared between groups. These outcomes should be based on what clinicians will find important when evaluating the treatment(s) and are

Box 3-1. Blinding in Action

An example of blinding is in the RE-LY study, which compared dose-adjusted warfarin requiring INR monitoring with two different doses of dabigatran etexilate not requiring INR monitoring. Researchers blinded the investigators to the group assignment by requiring all patients to show up for clinic follow-up visits but providing "sham" (or false) INR readings to the patients in the dabigatran groups and real INR readings to those in the warfarin group. In this manner, the clinicians did not treat the patients in one group differently from those in the other groups regarding the monitoring values because bleeding events and other safety parameters were also evaluated at these follow-up visits.

Information from: Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51.

	Outcome	No Outcome
Intervention	A	B
No intervention (control)	C	D

RR = (A/(A + B))/(C/(C + D)) OR = (A/C)/(B/D)

OR can be calculated in cohort studies (prospective) and case-control studies (retrospective), whereas RR can only be calculated from prospective cohort studies.

Figure 3-2. Basic 2 x 2 contingency table with RR and OR calculation.

decided ahead of time by investigators so that outcomes can be tracked and compared later. The key decision point investigators face that will affect the way the trial is conducted, measuring "surrogate" (i.e., proxy or "predictive" in nature) versus "real" outcomes, or both, as part of the study. Often, these types of outcomes can be delineated by something that affects the patient directly and measurably (e.g., stroke or mortality as a "real" outcome) versus something that is a measurement or observation but does not directly affect the patient (e.g., A1C for diabetes as a predictor of stroke or mortality).

Blinding must also be considered in trial design (Box 3-1). Treatment bias can have a significant effect on outcomes, particularly if outcomes are judged by clinicians or reported by patients. The study design must mitigate this type of bias. In non-blind (or "open-label") studies, all parties (patients, researchers, and third parties) are aware of the treatment allocation. Single-blinding a study generally means that either the patients or the investigators (but not both) are aware of treatment allocation. The term *double-blind* means that both the patient and the research personnel are unaware of the treatment assignment, and the term *double-dummy* means that when several dosage forms are being compared (e.g., a tablet compared with a subcutaneous injection), all groups receive a version (either placebo or active treatment) of all available dosage forms (Schulz 2002). With studies that involve third-party validation or input for the results (e.g., studies with radiographic evidence in which radiologists read radiographs), a "triple-blind" approach may be involved, meaning that the third-party personnel, patients, and study investigators are all unaware of treatment allocation (Misra 2012). In large studies with important safety parameters pertinent to appropriate patient care, researchers may choose a mixed approach to blinding.

Determination of Effect Size

One mechanism for placing research design into a clinical context is determination and interpretation of effect size, defined as the magnitude of difference between groups in a study (Sullivan 2012). The results of many summative statistical tests in a trial, and, at least in part, the final rejection or acceptance of the null hypothesis, is dichotomous – it either showed a benefit or did not. However, the magnitude of difference (effect size) should be considered when interpreting a study.

Relative risk is a measurement of effect size that is useful when comparing dichotomous variables such as mortality, cure rate, or whether some outcome is "present." The RR is calculated by dividing the probability of patients having the outcome in the intervention group by the probability of the outcome in the placebo or control group (Figure 3-2). A quotient (RR) of 1 indicates equal likelihood of the outcome between groups, whereas greater than 1 means a higher likelihood in the intervention group. A value of 0–1 favors the control group. Relative risk is generally appropriate for prospective studies like randomized controlled trials or cohort studies, in which patients are followed over time and observed for an outcome of interest.

Odds ratio is a type of RR typically seen in retrospective studies, in which the outcome of interest has already occurred. It is calculated by dividing the odds of the outcome in the intervention group by the odds in the control group (see Figure 3-2). When the incidence of an outcome is low (typically less than 10%), the RR and OR are very similar. As the incidence increases, the OR begins to differentiate (exponentially) from the RR and tends to exaggerate a risk or an effect of treatment (Figure 3-3). Both OR and RR are also typically accompanied by a 95% CI, allowing the ability to assess the sample's reliability to adequately represent the population. If the 95% CI of the OR or RR crosses the point of unity (1), the results are not statistically significant.

Power and Sample Size

Effect size is also important before a trial enrolling its first patient because an estimate or approximation of the effect size is used to determine how many patients will be needed to meet power (Charan 2013). Power is calculated as 1 – β (beta), β being the likelihood of a type II error. A type II error is the likelihood of a false negative – inappropriately accepting the

In a cohort study, 100 people who smoke and 100 nonsmokers were assessed for hypertension.

	Hypertension	No Hypertension
Smoking	65	35
No smoking	43	57

RR = [65/(65+35)]/[43/(43+57)] = 1.51
OR = (65/43)/(35/57) = 2.46

In this example, the OR overestimates the RR because the outcome (hypertension) was common (> 10%) in the group not exposed (nonsmokers).

Figure 3-3. Example of OR and RR with smoking and hypertension.

null hypothesis. In contrast, recall that a type I error is the likelihood of a false positive – detecting a significant difference when, in fact, one does not exist or inappropriately rejecting the null hypothesis. Sample size is directly related to power and effect size because when a study enrolls a large-enough sample size needed to appropriately accept or reject the null hypothesis, it is said to have "met power."

BIAS AND CONFOUNDING

Clinical studies assess the association of exposures or treatments on the development of disease or outcomes. Bias and confounding can threaten the accurate measurement of this association in studies. Bias is a systematic error in a study that yields an inaccurate estimate of the effect. In contrast, confounding is a natural phenomenon, independent of the study, in which a variable is related to both the exposure and the outcome.

Bias in Study Design

During study design, bias may be introduced with selection bias. Treatment-exposed and nonexposed subjects may be selected inappropriately, yielding inaccurate measures of association. This occurs because of a relationship between the exposure or outcome and the selection process (Pannucci 2010).

Selection Bias

Although selection bias is most likely to occur in case-control studies, it can also occur in prospective cohort or experimental studies. Patients lost to follow-up may be less likely to seek and/or maintain medical care and thus more likely to develop negative outcomes. In addition, loss to follow-up can occur because of adverse effects or intolerances, making treatments appear better than they actually are. A study design that performs and reports different types of analyses (e.g., intent-to-treat and per-protocol designs) in the results may limit this type of selection bias.

Box 3-2. Channeling Bias in Action

A case-control study of patients with rheumatoid arthritis was completed to assess a possible association of leflunomide, a disease-modifying antirheumatic drug, with the incidence of interstitial lung disease (ILD). Results showed an increased risk of ILD with leflunomide. However, when these results were stratified to identify patients without a history of methotrexate use, drug associated with lung injury, or history of ILD, the risk was no longer increased. The authors noted that patients at high risk of ILD appeared to have had channeling to leflunomide therapy, leading to the initial reports of the possible association.

Information from: Suissa S, Hudson M, Ernst P. Leflunomide use and the risk of interstitial lung disease in rheumatoid arthritis. Arthritis Rheum 2006;54:1435-9.

Channeling Bias

Often in a study, a patient may receive a particular drug because of perceived appropriateness of treatment. Channeling bias occurs when the severity of illness or other prognostic factors affect allocation (Pannucci 2010). This often occurs in newer treatments prescribed to patients whose older treatments have failed because of effectiveness issues or adverse effects. In studies with randomization, this issue can be avoided. An approach to avoiding channeling bias in observational studies is stratification of results, an example of which is shown in Box 3-2.

Bias in Study Execution

Data Collection Bias

A common form of information bias is misclassification bias, in which the misinformation leads to cases/controls or exposed/nonexposed being misclassified (Box 3-3). This

Box 3-3. Evaluating Potential Nondifferential Bias

A case-control study sought to evaluate the relationship of hormone replacement therapy (HRT) and risk of idiopathic thromboembolism. Cases were identified from a database using diagnosis codes. If patients without thromboembolism were accidentally coded as cases regardless of their HRT exposure, the association of the risk of thromboembolism with HRT would be artificially decreased. A manual validation review of a random 10% sample showed a lack of diagnosis of thromboembolism in only 1 of 30 patients suggesting a low likelihood of nondifferential misclassification.

Information from: Gutthann SP, Rodriguez LAG, Castellsague J, et al. Hormone replacement therapy and risk of venous thromboembolism: population based case-control study. BMJ 1997;314:796-800.

possibility emphasizes the importance of ensuring test or variable validity when designing or evaluating a study. Misclassification bias can be divided into two categories: differential and nondifferential. Differential bias denotes misclassification of treatment that is associated with the outcome and leads to a bias either toward or away from the null hypothesis. In nondifferential bias, the misclassification of the treatment is not associated with the outcome, leading to a dilution of measured association in both groups. Therefore, nondifferential bias leads to a bias toward the null hypothesis.

Misclassification bias can occur when interviewers are aware of either exposure or outcome when conducting an interview. This type is known as interviewer bias and can be avoided by masking interviewers as well as standardizing data collection tools, procedures, and staff training (Pannucci 2010). Misclassification can often occur when classifying patients as exposed or treated when adherence to medication is not sufficiently assessed. In addition, clinical outcomes may be misclassified when using diagnosis codes because they have variable accuracy in correctly coding true cases (Grams 2011).

Recall Bias

During an interview or survey, respondents may not accurately recall events, leading to misclassification of exposures, known as recall bias (Pannucci 2010). Patients may try harder to recall exposures, which could lead to falsely increased effect associations (Khoury 1994). Although using prospective cohort studies can minimize the occurrence of this type of bias, in a case-control study, it is best to discern and verify an objective measure of exposure.

Bias in Study Interpretation

Reporting Bias

After a study ends, one type of reporting bias commonly encountered is publication bias, in which studies with statistically significant results are more likely to be published than studies without (Hammer 2009). This topic will be explored more thoroughly in the section on meta-analyses.

Confounding

A common issue in study analysis and interpretation is confounding. Although a study tries to determine the association between the exposure or treatment and outcome, natural factors, known as confounders, not introduced by the study design, are associated with exposure or treatment and outcome that may not be readily apparent (Figure 3-4). A common example of confounding is the relationship between pancreatic cancer, smoking, and coffee. Coffee consumption (exposure) has a dose-related response to incidence of pancreatic cancer (outcome). Smokers often drink coffee (confounder), and smoking has been linked to pancreatic cancer. To accurately examine the effect of coffee consumption on pancreatic cancer, a study needs to address the confounding of smoking on the development of pancreatic cancer.

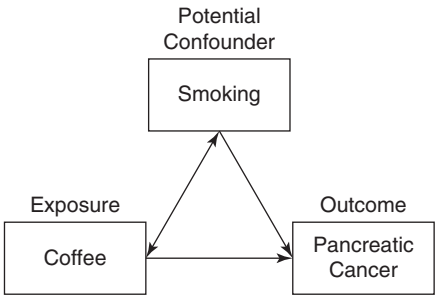


Figure 3-4. Example of a confounder's relationship with exposure and outcome.

Several different methods may be used to address the issue of confounding, including randomization, patient selection, and analysis methods (Hammer 2009). During the design phase, confounding may be addressed through randomization, the optimal method for controlling confounding, which should balance the confounders between comparison groups if the sample size is sufficient. However, randomization can only be used in non-observational (i.e., experimental) studies.

During the analysis phase, confounding may be addressed through stratification or multivariate analysis. Stratification analyzes results by confounding strata (e.g., age). In general, studies will create a mathematical model describing the relationship between exposure/treatment, confounders, and outcome(s) to yield an accurate exposure/treatment effect for an outcome (e.g., "adjusted" OR).

UPDATES IN CLINICAL TRIAL DESIGN

Systematic Reviews and Meta-analyses

Beyond the conclusions of individual studies, it is helpful to determine the summary of the literature for a particular topic. Methods used to summarize the literature include narrative reviews, systematic reviews, and meta-analyses (Bryant 2013). Narrative reviews cover general clinical questions without a clearly defined methodology of reviewing the literature and develop qualitative conclusions. These conclusions may be limited because studies included are based on author preferences. In contrast, systematic reviews incorporate predesigned methodology for selecting individual studies. Meta-analyses use data from individual studies that were systematic selected, and then the quantitative data are combined.

Reasons for conducting a systematic review and meta-analysis include conflicting individual studies, lack of sufficient power from individual studies to assess outcomes, and sample populations from individual studies not representing the overall population. However, the accuracy of a

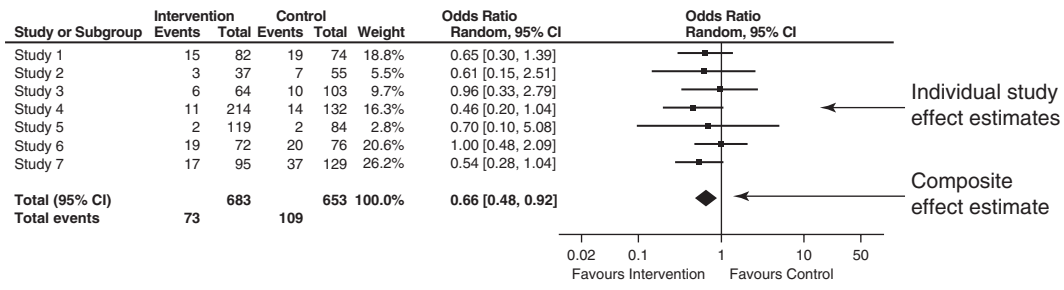


Figure 3-5. Example of a meta-analysis forest plot.

meta-analysis in describing the relationship of intervention and outcomes depends on the quality of the included studies.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline offers a checklist for conducting a systematic review and meta-analysis (Liberati 2009). Meta-analysis of Observational Studies in Epidemiology (MOOSE) and Quality of Reporting of Meta-analysis (QUOROM) are other reporting guidelines for meta-analyses in the literature, although the latter has been replaced by PRISMA (Brand 2009).

When planning a systematic review, a PICOS (participants, interventions, comparisons, outcomes, and study design) question should be defined. This question is used to define search criteria, which are queried in several secondary literature sources. Inclusion/exclusion criteria are defined to try to ensure a homogeneous patient population for analysis. Gray literature (e.g., unpublished conference proceedings) may be included and may remove publishing bias (McAuley 2000).

Once the studies for inclusion have been selected, the studies are assessed for quality, publication bias, and heterogeneity. Included studies are assessed using quality assessment tools, such as the Newcastle-Ottawa scale. Publication bias is assessed using methods such as the funnel plot (graphical) or Egger test (statistical significance $p<0.05$). If bias is present, this can suggest that the meta-analysis's effect estimate is inflated because of the absence of low or no effect studies (Sterne 2000). Heterogeneity, or variations in effect estimates that can be explained by differences in patient populations or methods across studies, is often evaluated using Cochran *Q* test or the I^2 index. The I^2 index is preferred when the number of studies included is limited because the *Q* test may lack sufficient power to detect heterogeneity in these cases (Liberati 2009). Heterogeneity among studies may be interpreted with a statistically significant *Q* test (generally statistical significance of $p<0.1$ rather than $p<0.05$ because of the low power of the test), whereas the I^2 index increases in percent as heterogeneity increases (e.g., 0–30 as low, 30–60 as moderate, 50–90 as substantial, and 75–100 as considerable).

After the individual studies are assessed, the effect estimates are combined and weighted by sample size per study. Depending on the heterogeneity or homogeneity of the included studies, either a random- or a fixed-effects model, respectively, is used to calculate the combined effect estimate. Characteristics of the included studies should be reported and include patient characteristics, sample size, study design, intervention, and any quality assessments made. Finally, results of the meta-analysis are graphically reported using a forest plot (Figure 3-5). Individual studies have sample-size scaled squares with CIs. When the CIs cross the vertical solid line (e.g., crossing 1 when reporting odds or risk ratios), the result is considered not significant. Below the individual studies, a diamond reflects the composite effect estimate.

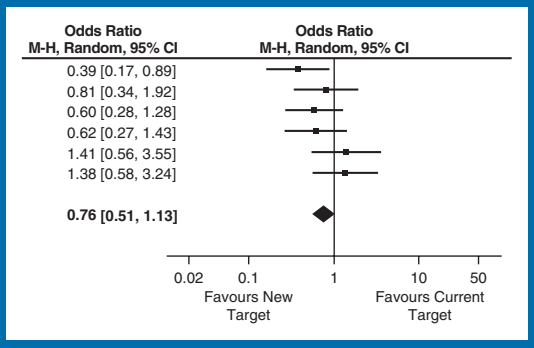
It is helpful to use established tools for evaluating the quality of systematic reviews and meta-analyses such as the assessment of multiple systematic reviews (AMSTAR) tool (Shea 2007). Considerations should be made if the authors followed established guidelines on conducting and reporting. Evaluations should be made on the generalizability of the included studies in the meta-analysis to the patient population of interest for clinical application. Specific principles for pharmacists for evaluating systematic reviews have been described (Haber 2015).

Adaptive Trial Design

About a decade ago, the FDA recognized the increased cost with developing medications without an increase in available therapeutics as a potential problem in ensuring effective therapy development (Chow 2014). One possible solution is the adaptive trial design. This study approach has been defined by the Pharmaceutical Research and Manufacturers of America (PhRMA) Working Group on Adaptive Design as a type of study that uses collected data to determine possible modifications to the study after initiation without disrupting study integrity. The FDA has supported this in a draft guidance by noting that adaptive design studies can prospectively plan time points to allow for modification of specific methodology (FDA 2010).

Practice Scenario

As clinical coordinator for your pharmacy department, you have been asked to serve on a multidisciplinary committee to revise the insulin drip protocols, specifically for cardiac surgery patients, because a recent large study with a new glucose goal suggested a mortality benefit compared with the current standard of care. A review of the literature shows several other smaller studies targeting the new glucose goal for these patients with mixed nonsignificant results. You decide to evaluate the summation of the literature through a meta-analysis and present the results to the committee for discussion. What checklist could you use to guide your process? How would you define what studies met your criteria? After combining the results using statistical software, what are two important things to test for to ensure an accurate effect estimate? Finally, using the forest plot that follows, determine whether the new target goals should be considered for replacing the standard of care on your protocol:



**Illustrative data, for example purposes only*

ANSWER

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist can be used to guide the process, including defining the patient population, intervention, comparison, outcome, and study design, to ensure appropriate study inclusion and exclusion. After combining the results, it is important to evaluate for publication bias and heterogeneity to ensure an accurate effect estimate. Moreover, it is pragmatic to do another a sensitivity analysis of only studies controlling for confounding through randomization, matching, or multivariate analysis to confirm the effect estimate again. Finally, a review of the forest plot shows that whereas the large study found a significant result (OR 0.39; 95% CI, 0.17–0.89), the other comparable, smaller studies led to an overall nonsignificant effect estimate (OR 0.76; 95% CI, 0.51–1.13), suggesting the current standard of care is adequate.

1. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6:e1000100.

The many different types of adaptive trial designs are divided by the FDA into two categories: generally well-understood adaptive designs with valid approaches to implementation and adaptive study designs whose properties are less well understood. The well-understood adaptive designs include adaptations of study eligibility, power, changes based on interim results of outcomes unrelated to efficacy, group sequential methods for early study termination because of either efficacy or futility, and changes in data analysis plan not dependent on between-group outcome differences. Less well-understood adaptive study designs include dose selection studies, randomization changes based on treatment responses, sample size changes based on interim analyses of efficacy, end point selection based on interim estimate of treatment effects, and adaptations in noninferiority studies.

Many benefits exist for using adaptive study designs. For example, using this approach can increase efficiency because outcomes can be achieved sooner. In addition, the odds of achieving a study objective are increased, thus decreasing overall study costs. When planning studies, assumptions are made about a particular study parameter (i.e., event rates). If a treatment effect is smaller than assumed, a trial can be successful by conducting a renewed sample size calculation and changing enrollment planning. Moreover, interim analysis allows for better characterization of treatment effect. In the absence or strong presence of treatment effect, this can allow for an early trial discontinuation (i.e., group sequential design studies).

There are many limitations with adaptive study designs. The FDA guidance suggests that possible changes should be identified a priori. However, this recommendation has been criticized because such issues are often unpredictable. Others have suggested that adaptive trial designs should allow modifications to be made concurrently or after the end of the study that were not preplanned. However, this increases the concerns for introducing bias and yielding possibly false-positive findings, a type I error. Conducting blinded analyses during adaptations may decrease type I error.

COMPARATIVE EFFECTIVENESS RESEARCH

Given the complexities of clinical trial design and the many aspects of trials important for interpretation (e.g., population studied, composite vs. surrogate outcomes), a simple "Is this

new drug or treatment better?" approach is often insufficient. For example, two treatments may have received FDA approval for the same condition but have not been studied head-to-head against one another. One of these treatments may be an injectable formulation given once monthly, whereas the other is an oral tablet taken daily. Independently, these treatments may have shown efficacy for the condition; the clinician, however, needs the critical information related to the comparative effectiveness of the treatments to make an informed and appropriate decision.

In addition, many large phase III trials for FDA approval may lack the context of having the current standard of care for a condition being included as a treatment arm. The study populations of many phase III trials may differ in significant ways from the populations that will eventually use the treatment in question. Often, the patients enrolled in these phase III studies, despite having the disease being treated, are otherwise healthy and may not adequately represent the heterogeneity of patients with complex comorbid conditions (Dasgupta 2010).

The Agency for Healthcare Research and Quality (AHRQ) defines comparative effectiveness research (CER) as "the conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat, and monitor health conditions in 'real-world' settings" (Velentgas 2013). The CER studies are designed to provide comprehensive evidence-based information to assist with point-of-care decision-making, particularly in distinguishing treatments from one another at the patient-level—translating population-based care into patient-centered care. Importantly, CER is not conceptually intended to provide cost-effectiveness information or limited to randomized controlled trials alone, though both may be aspects that, when analyzed in aggregate, assist an individual clinician with making the best choice of therapy for a specific patient.

History and Role of Regulatory Bodies

Although not a new phenomenon, CER has not been traditionally endorsed, emphasized, or otherwise addressed at the national level by governing bodies or regulatory agencies. The U.S. Food, Drug, and Cosmetic Act (FD&C Act), as amended in 1962 ("Kefauver-Harris Amendment"), which grants the FDA the authority to approve drugs for sale, requires sponsors to show the efficacy and safety of the product being submitted for approval (Katz 2004). Sponsors must demonstrate "substantial evidence" through "adequate and well-controlled studies"; however, this requirement does not include showing any type of relative effectiveness or comparison with any existing treatments. As a result, the FDA simply does not have the framework within the law for the systematic evaluation or facilitation of CER.

In 2003, section 1013 of the Medicare Prescription Drug, Improvement, and Modernization Act (MMA) authorized the creation of the AHRQ Effective Health Care (EHC) program, which came online in 2005 and began sponsoring CER studies. The original purpose and mission of the EHC was to "improve the quality, effectiveness, and efficiency of health care delivered through Medicare, Medicaid, and S-CHIP [State Children's Health Insurance Program] programs" (AHRQ). The MMA of 2003 also charged AHRQ and the Institute of Medicine with developing priority areas for CER, shown in Box 3-4.

Box 3-4. Initial AHRQ Priority Conditions for CER as Outlined by the IOM

- Arthritis and nontraumatic joint disorders
- Cancer
- Chronic obstructive pulmonary disease/asthma
- Dementia, including Alzheimer disease
- Depression and other mood disorders
- Diabetes mellitus
- Ischemic heart disease
- Peptic ulcer/dyspepsia
- Pneumonia
- Stroke, including control of hypertension

Information from: Institute of Medicine (IOM). Initial National Priorities for Comparative Effectiveness Research. Washington, DC: IOM, 2009.

The EHC program focuses AHRQ's efforts on establishing a baseline of knowledge in a given disease treatment area, identifying the gaps in research that are important to fill and assessing the clinical effectiveness of various treatments. The EHC also maintains a website with easy-to-understand summaries of available scientific information for consumers, clinicians, and policy-makers, as well as patient decision-making guides. A sample of the available published summaries is shown in Table 3-2.

An important recent milestone for CER in the United States was the American Recovery and Reinvestment Act (ARRA). Title VIII of this act provided significant additional funding to AHRQ, the NIH, and the Department of Health and Human Services for CER efforts (Vernon 2010). Although CER can and does often consider economic factors, CER is not exclusively composed of cost-effectiveness analyses. Another organization, the Institute for Clinical and Economic Review (ICER), ". . . evaluates evidence on the value of medical tests, treatments and delivery system innovations and moves that evidence into action to improve the health care system." The ICER is not directly affiliated with the U.S. government, but it provides independent evaluations of cost and effectiveness of interventions for various diseases. The prevailing political ideas behind the push for CER may have been focused on cost containment, but the ARRA did not specifically delineate or require the government to decrease the cost of health care or even slow its growth (Weinstein 2010).

Table 3-2. Selection of CER Analyses (Research Summaries) Published by AHRQ

Category	Consumer Summaries (Year Published)	Clinician Summaries (Year Published)	Policy-maker Summaries (Year Published)
Cancer	Treating Localized Prostate Cancer: A Review of the Research for Adults (2016)	Radiotherapy Treatments for Head and Neck Cancer (2015)	
Heart and Blood Vessel Conditions	Measuring Your Blood Pressure at Home: A Review of the Research for Adults (2012)	Venous Thromboembolism Prophylaxis in Orthopedic Surgery (2012)	
Mental Health	Medicines to Treat Alcohol Use Disorder: A Review of the Research for Adults (2016)	Off-Label Use of Atypical Antipsychotics: An Update (2012)	Depression Following a Traumatic Brain Injury (2011)
Muscle, Bone, and Joint Conditions	Managing Pain from a Broken Hip: A Guide for Adults and Their Caregivers (2011)	Comparative Effectiveness of Interventions for Rotator Cuff Tears in Adults (2010)	
Pregnancy and Childbirth	Progestogens to Prevent Preterm Birth: A Review of the Research About Progestogens for Women at Risk (2012)	Progestogens for Prevention of Preterm Birth (2012)	

Information from: Agency for Healthcare Research and Quality (AHRQ). Research Summaries for Consumers, Clinicians, and Policy-makers [homepage on the Internet].

Noninferiority Trials

Noninferiority trials have surged into popularity in recent years, given the push to increase the quality and quantity of CER (Schiller 2012). The basic tenets of design for noninferiority trials are similar to those for traditional "superiority" trials. However, key differences lie in the null and alternative hypotheses. Essentially, noninferiority trials set out to prove (i.e., the alternative hypothesis) that the intervention is "no worse" than the comparator(s), within the prespecified acceptable noninferiority margin (Oczkowski 2014). The null hypothesis, therefore, is that the intervention is *not* "no worse" than the control or comparator(s) – that the difference between the intervention and the comparator group exceeds the prespecified noninferiority margin (Schumi 2011). Importantly, failure to prove the alternative hypothesis does not mean that the treatments are equivalent, or that one is less effective than the other. The intervention simply fails to show that it is no worse than the comparator treatment and evidence is insufficient to reject the null hypothesis (D'Agostino 2003). Analogously, if the results of a superiority trial fail to provide sufficient evidence to reject the null hypothesis, it cannot be assumed then that the intervention and comparator groups are equivalent or noninferior (Wellek 2012).

A noninferiority trial may be preferred when a placebo-controlled trial would be unethical, or when the intervention studied provides a benefit that is difficult to measure or evaluate in a study, such as improved adherence (e.g., once- vs. twice-daily administration) or better safety profile (Piaggio 2006).

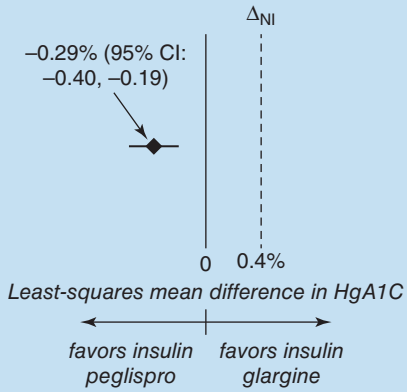
Noninferiority Margin

Noninferiority trials rely on appropriate selection of a noninferiority margin, usually represented as Δ_{NI} (Hahn 2012). Statistically, Δ_{NI} would reflect the maximum allowable difference between the groups that would favor the comparator. This is typically based on previous studies in which the active comparator was compared with placebo and is set at the upper boundary of the 95% CI of the difference; the final choice, however, should be based on sound clinical criteria and statistical reasoning (Christensen 2007). The margin should also be smaller than the minimum established clinical difference (effect size) between the comparator therapy and placebo (Lange 2005). In many cases, it would be appropriate to adopt strict margins for this so that the clinical relevancy is maintained, and that as much (or a significant portion, such as 50%) of the efficacy of the active control is maintained (Wangge 2010).

The FDA, which has published guidance for industry regarding noninferiority margins, continues to emphasize the importance of careful determination of this margin. When

Box 3-5. Example of Interpreting a Noninferiority Trial (IMAGINE 2)

Researchers conducted a phase III, double-blind, randomized, multinational study comparing insulin peglispro with insulin glargine, added to pre-study oral antidiabetic medications, in insulin-naive adult patients with T2DM. The primary objective was to test for the noninferiority of peglispro to glargine for least-squares mean change in A1C from baseline to week 52. A noninferiority margin of 0.4% for this change was chosen, according to published FDA recommendations. Results showed an A1C decrease of 1.6% in the peglispro group patients and a decrease of 1.3% in the glargine group ($p<0.001$). This resulted in a least-squares mean difference of −0.29% (95% CI, −0.40, −0.19). Because the upper limit of the 95% CI (−0.19%) is less than the pre-identified noninferiority margin (0.4%), peglispro can be considered noninferior to glargine in this study.



Information from: Davies MJ, Russell-Jones D, Selam JL, et al. Basal insulin peglispro vs. insulin glargine in insulin-naïve type 2 diabetes: IMAGINE 2 randomized trial. Diabetes Obes Metab 2016 Jun 28. [Epub ahead of print]; and FDA. Guidance for Industry. Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention [homepage on the Internet]. 2008.

sponsors submit materials for approval of new drugs or devices, the FDA expects explanations of any choices made related to noninferiority margins. Because the foundation of the choice of noninferiority margin is "clinical judgment," a substantial burden is placed on study designers, regulators, and practicing clinicians to be vigilant in both the practical use of the margin and the subsequent interpretation. A recent review found that almost 98% of noninferiority trials assessed (n=227) reported the noninferiority margin, but only 45.7% (106 trials) explained how the margin was determined (Wangge 2010). Even fewer (n=20; 8.6%) reported the margin as an acceptable clinical significance, whereas 22% (n=51) of the trials stated that the margin was based on researcher assumptions alone.

One of the main concerns related to noninferiority trials and of noninferiority margins, in particular, is the fear of "bio-creep," in which the efficacy margin for a new treatment proven noninferior to an active comparator becomes the standard margin of efficacy for the next generation of treatments (Gupta 2011). A new drug or medication could be approved with less efficacy than the comparator (within the prespecified margin, but still less effective). Theoretically, this could continue to occur until the treatments are no better than the placebo with respect to clinical efficacy. Many factors can affect bio-creep, including the choice of active comparator, underlying changes in the effect of the active comparator from trial to trial, and the distribution of effects of new agents (Stewart 2010).

Interpretation of Results

Given the parameters in the design of noninferiority trials and selection of the noninferiority margin, interpretation of these studies is slightly more complicated than for traditional superiority study design (Schumi 2011). The results should be viewed in the context of the noninferiority margin and therefore with reference to how that noninferiority margin was determined (e.g., comparison with a placebo control in a reference study). A result (including 95% CI) that falls within the acceptable range of noninferiority and does not include that point can be considered noninferior (Kaul 2007). A case study example in interpreting a noninferiority trial is shown in Box 3-5.

One consequence of noninferiority trial design is that, inevitably, several studies will refer back to and rely on the results of the same "active control" historical studies (Hung 2005). This would seemingly be in conflict with the FDA guidance for sponsors, which requires at least two studies to independently and conclusively show a new medication's efficacy. Study designers must pay attention to controlling the rate of type I error (i.e., false-positive rate) because this is key in developing the noninferiority margin and, consequently, how the results will be interpreted.

Equivalence Trials

Traditionally, equivalence trials have been used by sponsors of generic medications to prove that their products are no different (with an acceptable margin) from the branded (or trade) product, particularly in the realm of bioavailability, pharmacokinetics, and other absorption, distribution, metabolism, and elimination (ADME) characteristics. These trials have been termed *bioequivalence studies*, given their focus on biological, pharmacokinetic, or pharmacodynamic parameters (Jones 1996). In bioequivalence studies, a drug under development is studied and assessed in patients to determine whether its parameters are similar to those of a comparator drug, within a prespecified margin of equivalence. An example of this in a real-world study is shown in Box 3-6.

Box 3-6. Example Case of an Equivalence Trial

A recently published equivalence study evaluating needle length and size on glucose control in patients with diabetes and obesity provides a good example. This was a prospective, multicenter, randomized, open-label, two-period, crossover, equivalence study that included 274 patients and assigned them to receive insulin during the study period through a 4-, 8-, or 12.7-mm pen needle. The primary clinical outcome was change in A1C, with a prespecified equivalence margin of ±0.4%. The authors reported the source and determination of this margin from previously published data as an A1C standard deviation of 1%, meaning that the equivalence margin (±0.4%) would retain 60% (1 – 0.4) of the efficacy of the previously reported active control. This falls within the advised range of retaining at least 50% of the efficacy of the active control, as previously discussed with noninferiority trials; however, as an equivalence study, the investigators used a two-sided approach (±0.4%) vs. a one-sided approach with noninferiority trials.

Information from: Bergenstal RM, Strock ES, Peremislov D, et al. Safety and efficacy of insulin therapy delivered via a 4-mm pen needle in obese patients with diabetes. Mayo Clin Proc 2015;90:329-38.

Practice Points

As the landscape of clinical trial design evolves, pharmacists have a responsibility to remain vigilant in interpreting data to ensure the best patient outcomes. Some key points to remember are as follows:

- **Data can be described as continuous (interval or ratio) or discrete (nominal or ordinal), depending on the relationship between the individual points. Mean, median, and mode are all measurements of central tendency, whereas range, interquartile range, SD, and SEM are measurements of dispersion.**
- **Fundamental aspects of clinical trial design important for pharmacists to consider when analyzing trial design include patient selection, appropriateness of treatment(s), identification of key outcomes, and blinding (if present).**
- **Bias, systematic errors introduced into a study, as well as confounding, a naturally occurring relationship between a variable with treatment and outcome, are important concepts to consider when evaluating the medical literature because they can lead to inaccurate conclusions about the relationship between a treatment and an outcome.**
- **Systematic reviews and meta-analyses, qualitatively and quantitatively respectively, summarize the literature through predesigned methodology. The AMSTAR tool may be used to critically assess systematic reviews and meta-analyses.**
- **Adaptive trial designs allow for study modifications according to interim results. However, this can introduce bias; therefore, these studies must be evaluated carefully.**
- **CER includes studies and analyses that directly compare different interventions and strategies to prevent, diagnose, treat, and monitor health conditions. Governmental and regulatory involvement in CER was strongly stimulated by the ARRA; however, current laws do not require proof of comparative effectiveness before FDA approval.**
- **Noninferiority studies are different from traditional superiority studies because they are designed to test whether an intervention is "no worse" than a comparator. Failing to show evidence of noninferiority does not imply or prove equivalence or inferiority.**

CONCLUSION

The landscape of clinical trial design and interpretation has undergone tremendous change in recent years, with the development and enhancement of adaptive trial design, CER, and other changes in the regulatory environment. Practitioners must maintain vigilance in assessing new treatments and medications and in reassessing standard-of-care treatments for effectiveness.

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Self-Assessment Questions

41. A trial measures the effectiveness of an intervention in increasing 30-day adherence to daily medication regimens. The primary outcome is number of doses missed (e.g., 0 to 30). Which one of the following best represents the data types from this primary outcome?

    A. Ordinal
    B. Ratio
    C. Interval
    D. Nominal

42. A study evaluated how adolescents with or at risk of type 2 diabetes (T2DM) and their parent(s) value health states associated with T2DM. Investigators interviewed 12- to 18-year-olds with T2DM, prediabetes, or insulin resistance who were overweight or had obesity (BMI 85th percentile or greater) and a parent. The standard gamble method showed preferences (utilities) for seven hypothetical T2DM health states reported on a scale from 0 (dead) to 1 (perfect health). Adolescents and parents rated T2DM with no complications treated with diet as most desirable (median [interquartile range]; adolescent 0.72 [0.54, 0.98]; parent 1.0 [0.88, 1.0]) and end-stage renal disease as least desirable (adolescent 0.51 [0.31, 0.70]; parent 0.80 [0.65, 0.94]). Which one of the following best interprets the adolescent-specific results of T2DM with no complications treated with diet as most desirable?

    A. The average of all the values in the data set was 0.72.
    B. The 50th percentile of the data set was 0.54.
    C. The average distance of the points away from the central tendency was 0.44.
    D. 75% of the values in the data set were below 0.98.

43. A study of general well-being among patients with diabetes used a validated questionnaire. The questionnaire had respondents rate "0," "1," "2," or "3," with "0" reflecting "None of the time" and "3" reflecting "All of the time" to questions such as, "My life is pretty full." Patient results were grouped according to the type of diabetes treatment they were receiving. Which of the following best reports the difference in outcome measurements of the questionnaire ratings between groups?

    A. Mean
    B. Median
    C. Mode
    D. Interquartile range

44. A researcher is designing a study to test the effect of a new workout supplement on athletes' energy when weightlifting. She enrolls subjects for her study by sitting in the lobby of her local gym with a sign on her table and asking patrons if they are interested as they enter. Which one of the following best describes the sampling strategy this researcher is using?

    A. Random
    B. Systematic
    C. Convenience
    D. Stratified

Questions 45 and 46 pertain to the following case.

The LEAN study was a randomized, placebo-controlled phase II trial assessing subcutaneous liraglutide injections compared with placebo for patients who were overweight and had clinical evidence of nonalcoholic steatohepatitis. Over 3 years, the trial enrolled 52 patients, randomly assigning 26 patients to receive liraglutide and 26 to placebo. Patients, investigators, clinical trial site staff, and pathologists were masked to treatment assignment throughout the study. The primary end point was resolution of definite nonalcoholic steatohepatitis with no worsening in fibrosis from baseline to end of treatment (48 weeks). Nine of 23 patients (39%) who received liraglutide and underwent an end-of-treatment liver biopsy had resolution of definite nonalcoholic steatohepatitis compared with 2 of 22 such patients (9%) in the placebo group (RR 4.3 [95% CI, 1.0–17.7]; p=0.019).

45. Which one of the following modifications, if made by the LEAN study designers, would have most narrowed the CI and made the effect estimate (denoted as RR) more precise?

    A. Increase the number of patients enrolled.
    B. Change to a single-center study.
    C. Add another treatment arm.
    D. Change the end point to mortality.

46. Which one of the following best describes the type of blinding used in the LEAN study?

    A. Open-label
    B. Single-blind
    C. Double-blind
    D. Triple-blind

Questions 47 and 48 pertain to the following case.

Wenten et al., a retrospective cohort study of U.S. health care claims, evaluated the risk of acute pancreatitis with twice-daily exenatide versus other antidiabetic drugs. The study included patients without a history of pancreatitis in the previous 9 months who had a new claim for a diabetic medication during the 4-year study. Acute pancreatitis was identified with claims data through a diagnosis code placed in the primary position or noted as the main code. A total of 482,034 patients were included for analysis; after adjustments by

propensity score, the OR of pancreatitis with exenatide was 0.95 (95% CI, 0.65–1.38).

47. Wenten et al evaluated diagnosis codes not in the primary position, which led to pancreatitis event increases of 27% for exenatide-exposed patients and 39% for nonexposed patients. The authors decided that these codes lead to a potential bias based on an uneven proportional increase in pancreatitis among exenatide nonexposed patients. Which one of the following best describes the possible type of bias and implications on the study results?

    A. Differential bias that could lead to a dilution of measured association between pancreatitis and both exenatide-exposed and nonexposed patients due to higher rates in both groups. Therefore, no difference in outcomes would be seen overall, even in the presence of a difference in outcomes.
    B. Nondifferential bias that could lead to a possible lack of association between exenatide and pancreatitis because of a higher increase in pancreatitis events in patients not exposed to exenatide.
    C. Nondifferential bias that could lead to a dilution of measured association between pancreatitis and both exenatide-exposed and nonexposed patients due to higher rates in both groups. Therefore, no difference in association would be seen overall, even in the presence of a difference in outcomes.
    D. Differential bias that could lead to a possible lack of association between exenatide and pancreatitis because of a higher increase in pancreatitis events in the patients not exposed to exenatide.

48. Which one of the following is the best interpretation of the OR and 95% CI in Wenten et al?

    A. Pancreatitis was 5% less likely in the exenatide group, but this was not statistically significant.
    B. Pancreatitis was 95% less likely in the exenatide group, which was statistically significant.
    C. Pancreatitis was 5% more likely in the exenatide group, but this was not statistically significant.
    D. Pancreatitis was 95% more likely in the exenatide group, which was statistically significant.

49. Which one of the following proposed comparative effectiveness research (CER) studies would most likely qualify under the Initial Priority Conditions for CER, as outlined in the MMA of 2003?

    A. "Synthetic levothyroxine versus desiccated thyroid extract for the treatment of hypothyroidism."
    B. "Sildenafil versus tadalafil for the treatment of erectile dysfunction."
    C. "Oral tolvaptan versus intravenous conivaptan for the treatment of acute symptomatic hypernatremia."
    D. "Inhaled fluticasone/salmeterol versus oral roflumilast on prevention of chronic obstructive pulmonary disease exacerbations and hospitalizations."

50. Which one of the following best describes the role of CER in FDA approval of medications and devices?

    A. The FDA does not require outcomes of CER studies to be submitted and evaluated before approval of new drugs or devices.
    B. The ARRA required the FDA to evaluate CER on a new drug or device submission for approval.
    C. Drugs and devices must show superiority to currently available treatments or medications in order to obtain FDA approval.
    D. The AHRQ was granted authority to authorize FDA approval of medications and devices, depending on CER outcomes.

Questions 51 and 52 pertain to the following case.

The Hampel et al study was conducted to evaluate the effects of treatment with non-aqueous beclomethasone dipropionate (BDP) nasal aerosol on hypothalamic-pituitary-adrenal axis function in children with perennial allergic rhinitis (AR). Patients (age 6–11 years) were randomized (2:1) to beclomethasone dipropionate nasal aerosol at 80 mcg/day (n=67) or placebo (n=32). The primary end point in the study was change from baseline in 24-hour serum cortisol (SC) weighted mean for beclomethasone dipropionate nasal aerosol and placebo after 6 weeks of treatment. According to the results of similar studies, the SD of the logarithmically transformed data on the change from baseline (expressed as a ratio) in the 24-hour SC weighted mean was assumed to be 0.30. Noninferiority would be shown if the lower limit of the two-sided 95% CI for the geometric mean ratio of beclomethasone dipropionate nasal aerosol to placebo were greater than 0.80 (-0.2 from the point of unity of the ratio). After 6 weeks of treatment, geometric mean values were 6.19 and 7.13 mcg/dL, respectively, with no decrease from baseline in either group. The geometric mean SC ratio of beclomethasone dipropionate nasal aerosol at 80 mcg/day to placebo was 0.91 (95% CI, 0.81–1.03).

51. Which one of the following statements best reflects the alternative hypothesis (H_A) of the Hampel et al trial?

    A. The difference between the intervention and placebo groups exceeds the prespecified noninferiority margin.
    B. The intervention fails to show statistical superiority to placebo.
    C. The intervention is statistically superior to placebo.
    D. The difference between the intervention and placebo groups is within the prespecified noninferiority margin.

52. Which one of the following best portrays how the results of Hampel et al should be interpreted related to noninferiority?

    A. The study results met the requirements for noninferiority because the geometric mean SC ratio of beclomethasone dipropionate nasal aerosol at 80 mcg/day to placebo was greater than 0.80.
    B. The study results met the requirements for noninferiority because the lower limit of the two-sided 95% CI for the geometric mean ratio of beclomethasone dipropionate nasal aerosol to placebo was 0.81.
    C. The study results did not meet the requirements for noninferiority because the geometric mean SC ratio of beclomethasone dipropionate nasal aerosol at 80 mcg/day to placebo was greater than 0.80.
    D. The study results did not meet the requirements for noninferiority because the lower limit of the two-sided 95% CI for the geometric mean ratio of beclomethasone dipropionate nasal aerosol to placebo was 0.81.

53. Which one of the following best addresses possible confounding in a non-observational study?

    A. Stratification of results
    B. Multivariate regression model
    C. Randomization
    D. Discussion of study limitations

54. A researcher wishes to determine the risk of developing diabetes with statin use. Which one of the following methods would best determine the overall population risk?

    A. Narrative review
    B. Systematic review
    C. Meta-analysis
    D. Randomized controlled trial

Questions 55–59 pertain to the following case.

van Dam et al performed a systematic review and meta-analysis of the association of coffee consumption and risk of T2DM. The authors searched MEDLINE using the keywords coffee, diabetes, glucose, and insulin. Selecting for T2DM articles, nine cohort or cross-sectional studies were included. The risk of T2DM was RR of 0.72 (95% CI, 0.62–0.83) for 5–6 cups of coffee per day (moderate consumption) compared with the reference (0 cups per day for U.S. studies). In addition, the RR was 0.94 (95% CI, 0.88–1.01) for 3–4 cups of coffee per day (low consumption) compared with the reference. Heterogeneity was assessed using the Cochran *Q* test (authors set significance at $p<0.05$), with results of p=0.37 for moderate-consumption studies and p=0.09 for low-consumption studies. Publication bias assessed using the Egger test yielded p=0.62 and p=0.03 for moderate- and low-consumption studies, respectively.

55. Given the study type, which one of the following reporting guidelines would have been optimal and specific to observational studies for van Dam et al to follow?

    A. PRISMA
    B. AMSTAR
    C. MOOSE
    D. QUOROM

56. Given the reported testing for publication bias of the studies included, which one of the following best depicts the conclusion that can be drawn for the overall effect estimates calculated from van Dam et al?

    A. Publication bias is unlikely to be present.
    B. Publication bias may be present, but this should not be considered when interpreting the effect estimates.
    C. Publication bias may be present; thus, the true effect estimate is likely larger for low consumption.
    D. Publication bias may be present; thus, the true effect estimate is likely smaller for low consumption.

57. Given the reported heterogeneity testing of the studies included in van Dam et al, which one of the following is best to conclude, given the limited number of studies included?

    A. The analysis for heterogeneity accounted for the limited number of studies included, and the included studies lacked heterogeneity; thus, they were appropriate to combine in a meta-analysis.
    B. The analysis for heterogeneity accounted for the limited number of studies included, and the included studies contained heterogeneity; thus, they were inappropriate to combine in a meta-analysis.
    C. The analysis for heterogeneity accounted for the limited number of studies included, and the included studies lacked heterogeneity; thus, they were inappropriate to combine in a meta-analysis.
    D. The analysis for heterogeneity did not account for the limited number of studies included, and the included studies suggest possible heterogeneity; thus, I^2 would provide greater clarification.

58. van Dam et al analyzed the combined effect estimates (i.e., relative risk) using a random-effects model. Which one of the following best assesses this approach?

    A. The methods and patient populations across studies are essentially the same; thus, the approach is appropriate.
    B. The methods and patient populations across studies are essentially the same; thus, the approach is inappropriate.

C. The methods and patient populations across studies are varied; thus, the approach is appropriate.
D. The methods and patient populations across studies are varied; thus, the approach is inappropriate.

59. According to the reported results of van Dam et al, which one of the following is best to conclude regarding the association of coffee drinking and T2DM?

A. Drinking 3–6 cups per day of coffee may have a protective effect against diabetes.
B. Drinking 3–4 cups of coffee per day may have a protective effect against diabetes, whereas drinking 5–6 cups per day does not.
C. Drinking 5–6 cups of coffee per day may have a protective effect against diabetes, whereas drinking 3–4 cups per day does not.
D. The p values were not provided, so conclusions cannot be made.

60. A seamless phase II/III, adaptive, randomized double-blind study compared dulaglutide with sitagliptin or placebo in patients prescribed metformin. During the dose-finding stage of the study, patients were randomized 3:1:1 to seven different doses of dulaglutide, sitagliptin 100 mg, or placebo. According to the A1C response at 52 weeks, together with weight, heart rate, and diastolic blood pressure from week 26, dulaglutide doses of 1.5 mg and 0.75 mg were selected for further investigation. Further analysis showed the superiority of the dulaglutide 1.5 mg and 0.75 mg to sitagliptin 100 mg (A1C decreased by least-squares means of –1.10%, – 0.87%, and – 0.39%, respectively). Which one of the following is most likely to be a study limitation compared with nonadaptive study design?

A. Time to conduct
B. Cost to conduct
C. Characterization of treatment effect
D. Difference in bias

LEARNER CHAPTER EVALUATION: BIOSTATISTICS AND STUDY DESIGN.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

37. The content of the chapter met my educational needs.
38. The content of the chapter satisfied my expectations.
39. The author presented the chapter content effectively.
40. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
41. The content of the chapter was objective and balanced.
42. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
43. The content of the chapter was useful to me.
44. The teaching and learning methods used in the chapter were effective.
45. The active learning methods used in the chapter were effective.
46. The learning assessment activities used in the chapter were effective.
47. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

48. Apply various types of data to interpret study results.
49. Evaluate clinical trial design with respect to relevancy of end points, effect size, and sample size, as well as interpretation of noninferiority and equivalence trials.
50. Distinguish the role of bias in designing, conducting, and analyzing clinical trials.
51. Interpret the use of systematic review, meta-analysis, and adaptive design in clinical trials.
52. Analyze the role of comparative effectiveness research in regulatory approval and clinical interpretation.
53. Please provide any specific comments relating to any perceptions of bias, promotion, or advertisement of commercial products.
54. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Questions 55–57 apply to the entire Nephrology I learning module.

55. How long did it take you to read the instructional materials in this module?
56. How long did it take you to read and answer the assessment questions in this module?
57. Please provide any additional comments you may have regarding this module:

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